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“Whither Psychiatry?”

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IN the first place I would like to thank the Association for the great honour they have seen fit to do me in appointing me their President for the ensuing year. It is indeed a great honour and a sobering experience to occupy a presidential chair which has been filled in the past by such illustrious psychiatrists as Conolly, Maudsley, Crichton-Browne, Clouston, Mercier and Mott, to mention only a few. Not least amongst these names, one day I am sure will rank that of my immediate predecessor, Dr. Drury.

Sitting quietly one evening in my study thinking of a possible subject for this talk it came to me that dwelling as I did in a pleasant backwater near the banks of the Solway I was well placed for making a leisurely survey of the roads which psychiatry was travelling on both sides of the border. It seemed reasonable to hope that my survey would show me how psychiatry was tending and which of its many paths were showing the greatest promise. The result of these musings is this present address, which I have called “Whither Psychiatry?”

As I have no desire to suggest that my backwater is stagnant, I have considered it permissible to illustrate the various trends or aspects of psychiatry as far as possible by work carried out at the Crichton and of which therefore I have personal knowledge. My survey will be in no way systematic and still less exhaustive; rather will I follow the roads on which my local illustrations set my feet.

It seems logical to start with the query, Whither preventive psychiatry? Here there are many roads, but to me it would seem that all too many of the

people travelling some of them are talking rather than working. One can appreciate the aim of those to whom I particularly refer, namely, to alleviate the mental sickness not only of individuals, but also of societies and nations, and there is no doubt that some very sound work is being undertaken. Unfortunately, however, the movement tends to be brought into disrepute by those uncritical enthusiasts who give the impression that they have the key to a utopia from which war is banished, crime a thing of the past, and mental illness unknown outside text-books. According to some of them all that would appear to be required is that the rulers of the leading countries should through the personal analysis of themselves or their advisers know themselves and those they rule. I wonder. My own view of this is that while there is undoubtedly a place for psychoanalysis in group as well as in individual psychology, one has reason to ask for caution in its application to human relations, and still more to world affairs.

I am afraid our local efforts in preventive psychiatry have been on a more modest plane. The first example I would like to give is the Mental Health Survey of Dumfriesshire carried out by Dr. Mayer-Gross and Miss Brown, psychiatric social worker. It seems to me that this can certainly be regarded as a worth-while contribution to preventive psychiatry, in that it sets out very clearly the extent of the problem which has to be tackled as exemplified in a typical rural area. Probably the most striking information it unfolds is the very high proportion of backwardness in the school population viz., 11 per cent., and how utter is the failure to tackle this educational problem, to the consequent detriment not only of the dull and backward themselves but also of the normal boys and girls in our schools. It seems quite futile to prolong the schooling of these backward children beyond 14 years when it is apparent that they are incapable of benefiting by the type of education provided in the ordinary classes, which is usually all that is available to them. The fact that, as the Survey shows, these subnormals after leaving school seem to settle down into happy and contented citizens who do comparatively well as agricultural labourers, not only points the way to the practical type of education they need, but is further proof that their transference to this work should not be unduly delayed. While on the subject of education I would like to suggest a contribution our educationists could make to preventive psychiatry. In our materialistic age the emphasis is on such things as higher wages, shorter hours of work, higher standards of living, better housing, etc., and in keeping with this outlook education tends to be all too utilitarian in its aim. I feel strongly that the happiness of the individual is much more dependant on what he is than on what he has, and that accordingly it should be the aim of education to inculcate in the child a sense of values, religious, aesthetic and moral, which would enable him to live a full life in accordance with these values, and to make proper use of the abundant leisure which modern conditions provide. Certainly from the point of view of preventive psychiatry a person so educated should be better equipped to deal with the frustrations and other difficulties which lead to mental ill health in later life.

The Survey also showed that Mental Deficiency at 15.6 per 1,000 is appreciably higher than the 10.49 found in Lewis's Survey in three English Rural

Areas in 1927, which suggests that institutional and other provision for mental defectives may have to be even greater than at present envisaged. Another deduction which the cynic might draw from these figures is that it is probably time to replace the legend about the hard-headed Scot by one about the thick-headed.

Here I would like to suggest that similar surveys could be carried out with advantage by medical officers of health. The work would certainly enlighten them as to the nature and extent of their psychiatric problems, and our experience in Dumfries showed that they already possess much of the information required for such surveys.

Another important contribution to preventive psychiatry to which I would refer is the *education of the public* in matters psychiatric. I would like to relate an example of local activity which I think can claim to be in the nature of a pioneer effort. In 1948 the University of Glasgow in conjunction with the Education Department of Dumfries started an experiment in the holding of extra-mural classes on quite an extensive scale. Short courses in social science, child guidance and psychology proved so popular that last year the Crichton agreed to organize a complete course of lectures dealing with mental health in the community. The course was spread over the full six months of the Extra-Mural Session and consisted of 20 weekly lectures given by 16 different lecturers, all authorities on their subject, and including the Professors of Psychiatry in the Universities of Glasgow and Durham. The course was attended by more than 80 people, including teachers, general practitioners, public health and other nurses, business men and women, mostly people interested in social welfare in its many branches. That interest in the course was sustained to the end was shown by an enthusiastic audience of over 200 at the final session, which took the form of a brains trust. The primary aim of the course was to give to its members a background of knowledge which would enable them to take an active part in fostering public interest in mental hygiene. After each lecture the members arranged themselves in discussion groups of eight to ten under group leaders and proceeded to discuss questions suggested to them by the lecturer. They were encouraged to examine and relate the lectures to their personal and professional experience, so that the group got the advantage of the experience of its various members for practical application at a later date when putting into use what they had learnt at the course. I think it will be agreed that this attempt to interest and educate these influential members of the public in mental health is a contribution to preventive psychiatry worthy of development.

A path closely allied to, if not identical with, that of preventive psychiatry is that of *early treatment*. In England this path broadened out into a public highway in 1930 with the passing of the Mental Treatment Act, and it is hoped that following the Russell Report a similar Act for Scotland will not now be long delayed. Thirty years ago, when our mental hospitals had little better to offer than custodial care, this question of early treatment had not the importance it has to-day, when so much can be done by psychotherapy and the modern physical methods of treatment. Here I think we can congratulate ourselves on the lessening of the schism in our ranks which these two discip-

lines have tended to foster. Always there has been the tendency for the psychiatrist who has not practised psychotherapy to belittle it, while his opposite number with no experience in physical methods has often described them as little short of criminal. Nowadays the number of psychiatrists with experience of both methods is ever increasing, and it is rare for anyone so trained not to appreciate the advantages and shortcomings of both methods. While on the subject of psychotherapy I would like to record my opinion that the more it is appreciated that the fundamentals of psychotherapy, like the skill in their application, belong to the art rather than the science of medicine, the more will be its progress and the greater its scope of usefulness.

Looking ahead on the highway of early treatment, it seems to me that our task as an Association is to encourage the provision of facilities for early treatment, and to make sure that the quality of the treatment provided is of the highest. A great advance in this matter of early treatment will undoubtedly come from the Chairs of Psychiatry recently instituted in several universities both in Scotland and England, and I am sure that psychiatry as a whole will benefit greatly from the psychiatric units and other activities which have been set up by these Universities in their respective regions.

So much for the roads along which preventive psychiatry would appear to be travelling. Some are broad, some narrow and some more promising than others, but it can safely be said that steady progress is being made in their construction and in the journeys along them.

The next roads which I envisage and on which I would now like to linger are those belonging to *Child Psychiatry*. Born across the Atlantic, this child of our speciality is slow to form roads characteristic of British rather than American Psychiatry. It still retains its team attack, which is undoubtedly excellent, but on the other hand its expense has certainly slowed up its expansion. All members of the team, psychiatrists, psychologists and psychiatric social workers are in short supply, and look like being so for a long time to come, yet any form of dilution seems to be anathema to the vast majority of those employed in the work. Surely there is at least a growing place for the highly trained lay psychotherapist willing to work under proper medical supervision. More American than British also is the tendency in child psychiatry for undue emphasis to be placed on the psychoanalytic approach. While fully agreeing with the dictum that the child is a child and not a miniature adult, it is still my strongly held opinion that child psychiatry is not in any fundamental way different from adult psychiatry, and this being so I cannot agree with the psychoanalytic claim that theirs is the only rational approach to the maladjusted child. It is usually claimed that some 70 per cent. of those who attend child guidance clinics are helped by so doing, and I look forward to the day when we will be presented with a comparative study of the results obtained in child psychiatry by the various forms of approach, including that of psychoanalysis. Equally with the psychoanalyst other child psychiatrists appreciate the importance of the early stages of a child's development in shaping its personality, and like them they know that the interaction between biological and cultural forces, between nature and nurture, is all important in this development. I would suggest that this

agreement should give sufficient common ground to allow child psychiatry to develop its different methods of approach and clinical practice with every confidence that its future progress would be abundantly assured. In-patient clinics for maladjusted children are a comparatively recent development in this country. Portsmouth and the Maudsley have had such clinics for some years, and we in Dumfries have recently started the first one in Scotland. It is interesting to report that this unit had its being as a result of a request from the Scottish Division of our Association to the Western Regional Hospital Board. Such units are likely to multiply in the near future, and in addition to the treatment of their patients they should offer valuable opportunities for research into problems of behaviour and the psychoses, as well as being extremely useful for post-graduate teaching in child psychiatry.

TREATMENT.

The next road I approach is that relating to *Treatment*. It is a wide road with numerous branches, many of which I must leave unexplored. The shock troops, of course, are prominent, a comparatively young body, though some critics would fain class them as direct descendants of others of the early nineteenth century whose armamentarium included such things as revolving wheels, surprise baths and swinging beds. Some of the more vocal of these critics are psychotherapists who are quite genuine in their protests and in their belief in the superiority of psychotherapy even in the psychoses. Unfortunately there are still a few who use the same destructive arguments, not to justify their particular form of treatment, but as far as one can judge largely to excuse their negative attitude to *any* form of active treatment. While on this subject I would like to say that I have little sympathy with those who give lack of nursing staff as an excuse for the withholding of some of these forms of treatment. As far as the supply of nurses is concerned it has been my experience that these treatments do not necessitate any appreciable increase of nursing staff. I find that the staff required to administer occupational, recreational and insulin therapies are largely saved in the greater ease of nursing the patients who have been improved by such treatment. It is usually considered that the heaviest drain on nursing staff is in the admission wards with their unknown quantities amongst the patients. It might therefore be expected that with its high admission rate of over 1,000 patients per year for its 1,200 beds the Crichton would have a high nurse-patient ratio, and particularly as in addition to its 15 occupational and recreational therapists it has 13 nurses engaged whole time in the Occupational and Recreational Therapy Departments, and 9 in the Insulin Department. I am firmly convinced that it is because there are so many nurses engaged in these active therapies that the optimum nurse-patient ratio is fixed so low as 1 to 5.1.

Be that as it may, we can certainly maintain that thanks to psychotherapy and the physical therapies psychiatric treatment has improved out of all recognition in the last three decades, and I think we can claim greater advances during that time than during any other comparable period. It may well be that our present shock therapies will appear somewhat crude to a future

generation. Certain it is that medicine abounds in records of empirical treatments, later replaced by something more specific. For example, cinchona bark was long used in the treatment of malaria before being replaced by elegant preparations of its active principle, quinine, and fresh vegetables only recently gave pride of place to the vitamins in the treatment of scurvy and other deficiency diseases. In the same way more specific treatment may well replace our present shock methods if only we can discover what in fact is their active agent. It is my firm conviction that these various shock treatments differ quantitatively more than qualitatively, and if this be true the future may well see great refinements in their application. These remarks are not meant to belittle the extremely good results which we are presently obtaining. A recent follow-up carried out at the Crichton on all patients who had received one or other of the physical treatments during the years 1939 to 1947 disclosed many interesting facts of an encouraging nature. Like the majority of such investigations, both here and abroad, it provided abundant evidence that clinicians who practise these treatments are fully justified in so doing. I hold very strongly, as I have for many years now, that the facilities for these treatments should at least be available to all psychiatrists who wish to treat their patients by them. If they do not wish to employ such methods they need not, but equally if they do wish to they should have the facilities so to do. As you know, the hypotheses offered in explanation of how these empirical shock therapies work are legion. I do not propose even to enumerate them, but perhaps I will be excused for describing in some detail the biochemical one which I favour. It is of course well known that all shock treatments cause cerebral anoxia, and as in the hypothesis I am putting forward this phenomenon plays an important part, it is probably advisable that I clarify my views about it.

We know that for all practical purposes the only substance which the brain cells can utilize is glucose, and further that its oxidation necessitates the presence of oxygen and the catalyst dehydrogenase. Strictly speaking anoxia means lack of oxygen, but biochemists have extended the use of the term to include conditions where the same results are obtained by inability to use any oxygen present. Thus in the present context anoxia may be due to lack of oxygen, lack of glucose or lack of dehydrogenase. In actual fact one or other of these forms of anoxia takes place in the various shock therapies. Thus in nitrous oxide and CO_2 therapies the available oxygen is used up; in insulin therapy the available glucose; while in prolonged narcosis the catalyst is rendered unavailable by the attachment of the narcotic to it. Electrical convulsion therapy causes its anoxia by excessive cerebral activity using up the available glucose, while at the same time cessation of respiration interferes temporarily with the oxygen supply to the brain. That cerebral anoxia is not sufficient in itself to explain how the shock therapies bring about a cure is shown by the fact that merely taking our patients up into high altitudes or placing them in decompression chambers does not cure them. I would suggest that the various therapies are selective in the site of their cerebral actions and that this may be one factor in their therapeutic results. Thus we have both clinical and *in vitro* experiments to show that different barbiturates

act on different parts of the brain, and there is abundant clinical proof that insulin and E.C.T. act in this selective fashion. In fact various hypotheses of their efficacy claim that this is due to selective action on the autonomic system, the pituitary mechanism or the reticular system of the thalamus, to mention only a few. I feel I have been on reasonably firm ground so far, but fear there is less practical evidence in support of the remainder of my hypothesis. This postulates that in the psychoses cerebral metabolism is acting below its optimum due to a partial upset of its oxidation systems, e.g., by circulating amines not detoxicated by the liver, as suggested by the benzoic acid tests of Quastel in catatonics and the work of Gjessing and others. It is quite possible that this upset may sometimes be the continuing result of a causal agent which itself has ceased to be active, which incidentally might explain the inability of Richter and others to find any toxic amines in the blood of various types of psychotics. The hypothesis further postulates that when the metabolism of the brain is recovering from the anoxia caused by the treatment, at least temporarily it returns nearer to its optimum, and if the treatment is repeated often enough it tends to retain this higher level with a resultant cure of the psychosis. In short it is not the anoxia but the brain's reaction to it that restores normality. I like to think that this latter part of the hypothesis fits in with Cannon's concept of the homeostatic principle, and that a homeostatic centre may even be involved in the operative mechanism. If this hypothesis is correct one would expect a cure to be most likely in those cases referred to above in which the lowered cerebral metabolism is the result of a causal agent which is no longer active. This offers an explanation of the occasional failure of E.C.T. at the beginning of a depression and its success later when, it may be, we are dealing with the end-result of our unknown causal agent. Again, as sepsis can cause cerebral anoxia, we have here a possible explanation of the well-known fact that tonsillar and other forms of sepsis may interfere with the efficiency of insulin therapy and E.C.T. The hypothesis can also be used to explain why the longer and much more frequent anoxia of insulin therapy is required for schizophrenia, whereas E.C.T. is sufficient for the less malignant manic-depressive psychosis. It is quite impossible to prove or disprove these speculations till much more is known of the biochemistry of the C.N.S., and unfortunately this is such a difficult subject that biochemists seem to fight shy of it. We are still largely ignorant of the biochemistry of the healthy nervous system, and accordingly it is extremely difficult at present to carry out really fundamental investigations into the biochemistry of the neuroses and psychoses—in short a knowledge of physiology must precede a study of pathology. I hope I may be excused yet another speculative diversion, this time into a by-way which one day may constitute an important psychiatric highway. Is it possible that the theory of adaptation diseases put forward by Professor Hans Selye in his Heberden Oration for 1950 contains something of importance for psychiatry? Certain it is that many of our psychoses, including schizophrenia, fit in well with his concept of an adaptation disease as a biochemical or metabolic disorder due to physical or emotional stress, and with a reversibility which may occur from some biological change brought about spontaneously, therapeutically or

accidentally. Is it possible that some substance of the nature of cortisone or ACTH may be forthcoming as a therapeutic agent in the psychoses? Professor Selye has described how ACTH failed to cure certain mental patients where subsequent shock therapy succeeded, and he went on to postulate that the latter had caused certain specific changes which had acted as conditioning factors of the pituitary-adrenal discharge characteristic of the general adaptation syndrome. This hypothesis certainly brings shock therapy into line with the adaptation reaction, and advances the possibility of ACTH and cortisone being the forerunners of non-specific shock therapies superior to those we at present possess.

RESEARCH.

I would now like to pass from the comparatively straight wide road of physical treatments into the much vaguer and more indeterminate pathways of research, and first I would like to travel the *biochemical* one. I must confess to a partiality for this road, as rightly or wrongly I have always felt that it was the most hopeful of all approaches to psychiatry and the one most likely to repay extensive research. In my Cardiff days I often remarked that if half the time and money spent on cancer research alone were spent on biochemical research in psychiatry, the benefits which would accrue to mankind would be profound. I am still of that opinion.

Even to-day very few laboratories are tackling the problem on the scale started by Quastel at Cardiff City Mental Hospital, and I have always deeply regretted the necessary interference by the war in his pioneer work on the carbohydrate metabolism of the brain. I am pleased to say that Dr. Richter, his successor at Cardiff, has some very promising work in hand from which important results may well accrue in due course. I would like to pay my tribute here to the valuable work that is being done in many small biochemical laboratories attached to our mental hospitals in different parts of the country. From the small Crichton laboratory Mayer-Gross and Walker recently published interesting results on the restoration to consciousness of patients in insulin coma by the injection of glutamic acid and other amino-acids, work which suggests that the brain may when necessary utilize foodstuffs other than glucose. Weil-Malherbe considers that the results are due to adrenaline produced by the hypoglycaemia, but Dawson, working in Richter's laboratory, obtained results which make this a very unlikely explanation. Too little is known, however, to decide if there is in fact a direct utilization of the glutamic acid by the brain cells. At present the Crichton laboratory is investigating the claim of Meduna to have isolated a hypoglycaemic factor in the urine of certain acute schizophrenics. We have been successful in isolating the substance and examination of controls naturally followed. Since finding that he himself is positive to the test Mayer-Gross has doubts as to its complete specificity: and so it goes on. One day the biochemical explanation of such things as schizophrenia is just round the corner, the research continues and the final arrival is not at a terminus but at the siding of some small wayside station. Such is the fate of most research, but so long as it is critically scientific it is a contribution to knowledge and accordingly of definite value.

A well-trodden if narrow road of older date than the one we have just left is that of *Neuropathology*. If the biochemists have been afraid of the nervous system the same cannot be said of the histologists, and as a result a long line of brilliant neuropathologists have thrown light on those less common diseases of the nervous system which bring organic changes in their wake. For help in understanding the commoner psychoses such as schizophrenia and the manic-depressive group it would appear that we must await new methods of approach and the improvement of existing methods. The ever-growing co-operation between neuro-anatomists and neuro-physiologists with their delicate electro-physiological techniques have been corroborating the claims of the former that structural differentiation in the C.N.S. is evidence of corresponding functional differentiation and localization. At present amongst their other activities Professor Meyer and his Maudsley school are guiding us in the dark places where leucotomy leads, and as so often happens in medicine the members of the team, in this case the neurosurgeons and the neuro-pathologists, are providing each other with valuable material for benefiting their respective specialties. It is only recently that the Scottish neuropathological road was re-opened at the Crichton by Dr. Klein, yet another pupil of the German school of neuropathology, and we are hoping that it will be carrying a little traffic, at least, in the near future.

From the highway of *Biophysics* on which the, to me, well-beloved figure of Professor Golla is particularly prominent, probably the most important road as far as psychiatry is concerned is that relating to electro-encephalography, with its use of biophysical methods to amplify and record the small variations of electrical potentials in the brain. While most of its traffic centres on Bristol and London, of recent years much activity has been apparent in other parts of the country. While we are justified in expecting great developments in this sphere of activity, it is unfortunately true that the light thrown on most psychiatric problems is still disappointingly slight. Nothing of fundamental importance has been added to our knowledge and understanding of the major psychoses or neuroses, but on the other hand we certainly continue to receive valuable additions to our knowledge of epilepsy, psychopathic personality and some organic disorders. Special mention must be made of the valuable contributions of Grey Walter, Denis Hill and their co-workers. In continuing my practice of using local illustrations I would point out that it was at the Crichton that Roth did his original work on the changes in the electrical activity of the brain induced by E.C.T. In the paper he is reading to-morrow he brings evidence to show that E.E.G. changes occurring during treatment are due to electrical activity in the frontal lobes caused by the cumulative stimulation of a subcortical pacemaker situated in the thalamic reticular system, and he puts forward the hypothesis that this thalamic stimulation is the causal factor which ultimately leads to the recovery which results from E.C.T. There is no doubt that the E.E.G. changes recorded by Roth do take place, but whether they are merely concomitants of the E.C.T. or the actual curative factors must await further investigation. Certain it is, however, that such work goes to show the intriguing possibilities of E.E.G. research.

Another road which centres on Bristol is that dealing with *Endocrinology*. This is a line of research which held out great promise, but in spite of the painstaking work of such as Reiss surprisingly little seems to have come out of it. One reason for this is undoubtedly our aforementioned lack of knowledge of the biochemistry of the brain, which makes it extremely difficult to correlate cerebral changes with hormonal activities, normal and otherwise. It is certainly work which has great possibilities, and it is to be hoped that one day soon new methods may be evolved which will yield a richer harvest. Is it possible that the plethora of facts so painstakingly collected will one day be found to fit in with the work of Professor Selye already mentioned, and help to further its application to those psychiatric disorders which may turn out to be due to hormonal derangements resulting from maladaptation to stress?

Here we leave Research and approach the last road on which I will take you, that of *Academic Psychology*. This is a wide road, which in former days was probably even more travelled in Scotland than in England.

From the days of Hume more than 200 years ago up to quite recently Scottish psychology had a distinctive national character, thanks to such exponents as Adam Smith, Thomas Reid, William Hamilton, Alexander Bain, and more recently G. F. Stout. Scottish psychology always had a metaphysical background, and there are signs that, invigorated by its recent Freudian mud-bath, psychology in general is returning to its former relationship with metaphysics and moral philosophy, all the better for its incorporation of such concepts as symbolism and unconscious phantasies. This development is likely to be encouraged by the tendency of social psychology to break with the older static psychology, and join with the anthropologists and sociologists in the new discipline of social relations. At the Crichton we have a Psychological Research Department which is affiliated to the University of Glasgow. Much of the work of the Department is carried out in relation to clinical psychiatry, but much relates to the wider sphere of scholastic, industrial and academic psychology.

The measurement of abilities and aptitudes in personnel is playing an increasing role in education and industry, and Raven and his co-workers at the Crichton are making important contributions in both these fields, using along with other methods the various matrices tests which they have evolved.

As some of the papers to be read to-morrow will show, the Crichton psychologists have joined with the psychiatrists in research into such matters as the structure and dynamics of the personality at various ages and the effect of different treatments in the various psychoses. His appreciation of the science of statistics and his training in the treatment of psychological data and methods of psychological research make the psychologist an indispensable member of the psychiatric research team in such problems. The great advantage of having psychological research departments capable of fundamental research attached to such hospitals as the Maudsley and the Crichton is that it is possible to carry out clinical research of a very high standard. Such a department would be failing in its true function if, in addition to research which could be carried out equally well at a University or special research centre, it did not include in its programme an appreciable amount of clinical

research which required material and facilities which only the mental hospital or psychiatric unit could provide.

So we come to the end of our wanderings. I would again emphasize that what I have been offering you this afternoon is not a studied survey of the whole field of psychiatry. For example no mention has been made of such vitally important matters as the recently enacted Criminal Justice Bill and other Acts which embody enlightened psychiatric opinion, and are destined to guide psychiatry in relation to such things as the prevention and treatment of delinquency in the young and crime in the adult. Again I have seen fit to exclude from my survey the National Health Service with its great potentialities to influence, for good or evil, the future of psychiatry. Nor have I given any indication of my opinion on such an important subject as the probable course and ultimate fate of orthodox psychoanalysis in this country.

Apart from any other consideration the time at my disposal this afternoon has precluded the feasibility of a fuller survey, but honesty compels the confession that an even more important reason is my complete unfitness for the task. I always think there is no harm in confessing the apparent. Again it will be noted that in posing the question "Whither Psychiatry?" I have made little attempt to answer it. What I have attempted is to give a few personal impressions of some of the trends in the world of psychiatry today. I ask you to excuse the all too free use I have made of local illustrations. I appreciate that this has inevitably led not only to glaring omissions but to a somewhat unbalanced review.

In conclusion I would like to put on record my confession of faith in the future of our speciality. In my opinion we can look back with justifiable pride on our progress during the past three decades, and we can look forward with equally justifiable optimism to steady progress in the future. Let us be never failing in our co-operation with the great body of general medicine to which of course we indissolubly belong, but let us equally never forget that progress in our speciality, in the future as in the past, will come mainly from the efforts of those actually engaged in the practice of psychiatry and in research into its special problems. In short, let us continue to stand on our own feet. Ladies and Gentlemen, I thank you.

POST-OPERATIVE SYNDROMES IN SELECTIVE PREFRONTAL SURGERY*

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THE prefrontal region lies in front of the motor and premotor areas of the frontal lobe. In Brodmann's terminology this corresponds to areas 8, 9, 10, 45 and 46 on the convexity; 11, 47 and 13 on the orbital surface; 24, 32 and 12 on the mesial surface. When speaking of selective prefrontal surgery, we mean topectomy or cortical undercutting or partial leucotomy of one or several of these areas.

In a preceding paper (7) the difficulties of performing a really selective operation have been discussed; topectomy was advised in most cases for reasons of both safety and selectivity, but cortical undercutting was considered advantageous in patients over 60 years of age. In cortical undercutting an additional difficulty arises in that following even very slight changes in the position of the head variations of site occur. It is absolutely necessary to check the extent of any type of operation by X-ray study of such landmarks as clips or gelfoam with lipiodol. Thus, it was felt, a method has become available for evaluating statistically the possible correlations between anatomical lesions of areas variable in size and the clinical consequences of the operation.

Since the beginning of psychosurgery two theories have been developed to explain the action of the operation, which, generally speaking, might be called the quantitative and qualitative theory respectively. However, little concrete research had been done in this respect before publication of an important paper in 1949 by Meyer and McLardy (14). These authors arrived at the conclusion that "whatever tendency there may be for any degree of localization is, so far, overshadowed by a quantitative relationship between the degree of personality change and the amount of prefrontal cortex cut off." However, as the authors themselves admitted, their material was made up of patients submitted to extensive lobotomies who had been suffering from complex psychotic states; the conclusions might have been different if selective operations performed in simpler conditions, such as cases of intractable pain, anxiety neurosis or psychomotor agitation had been analysed (9, pp. 1550-1).

For a long time our own work has been directed towards demonstrating eventual differences of function corresponding to different prefrontal areas; such differentiation seemed likely in view of their relative individuality in structure and connections (5, 8 and 9). Recently the *long-term therapeutic results* have been analysed for a series of 100 selective prefrontal operations (7). In this paper we present the clinical differences between the *immediate post-*

* This paper, together with a previous one (7), contains essential parts of a lecture given at the Maudsley Hospital on 31 May, 1951.

operative syndromes following 134 topectomies and selective leucotomies in various locations. So far no special psychological investigations are available for publication. The present paper, therefore, is based on rather crude observations of obvious behaviour disturbances, such as confusion with disorientation in time and space, apathy, agitation, euphoria, depression and their customary emotional expressions and, finally, vesical and rectal incontinence.

Sometimes the post-operative syndrome is very slight or lasts a few hours only; such cases will be considered as normal. However, there is usually little difficulty in diagnosing it as a clinical entity when it lasts several days or, as is usual, one or two weeks, or even, as is more rare, six to eight weeks. It is not exceptional to see it appear one or two days after the operation and to reach its maximum about 10 days later, then to fade away progressively. In all our patients the post-operative syndromes were transitory, in contrast to what is so often observed after the posterior cuts of the classical lobotomies.

The total number of cases in the present study is 134, but not all lend themselves to a useful analysis. We have omitted three categories: (a) 8 early fatalities, (b) 8 mentally very backward individuals, (c) 10 unilateral operations not followed by any significant clinical change; these were unilateral topectomies or undercuttings, or unilateral lobotomies, with cuts always at least 2 to 3 cm. in front of the coronal suture.

Thus we were left with a series of 108 bilateral prefrontal operations, all in front of area 8, whatever their mesial or lateral extension; of this material 81 were topectomies, and 27 "leucotomies" (the distinction between a very rostral lobotomy and an apical cortical undercutting is not always easy).

A first conclusion stands out with little doubt: *there is a great difference in post-operative behaviour between the "convexity" and the "mesial" patients.* Of 76 operations involving the convexity and/or the orbital region, 40—more than half of them—were followed by a marked post-operative syndrome, whilst of 32 mesial operations, only 4 were followed by definite behaviour abnormalities. The difference seems significant and, we believe, constitutes a strong argument in favour of the qualitative theory. Presumably the extent of cortical resection or isolation as checked by radiography is on the average not very different in these two groups. That the mesial surface of the prefrontal lobe and its convexity do not have the same function with regard to behaviour is not entirely unexpected: one could not fail to observe, for instance, the striking disorder of behaviour following a bilateral prefrontal lobectomy for an olfactory meningioma, whereas, in marked contrast, the post-operative syndrome following removal of a glioma invading the anterior corpus callosum and the mesial walls of both frontal lobes is far less conspicuous (20).

A more detailed analysis of the post-operative syndrome is now possible according to the location of our selective resections:

1. *Convexity Operations.*

Our results are shown in Fig. 1, which is a diagram similar to the one already published (7) on the therapeutic effects. The numbered levels correspond to the *mean* lengths of some prefrontal areas, as measured by Beck, McLardy and Meyer (2): from -5.5 to -4 = area 13; from -4 to -1 =

area 11; from — 1 to 4 = area 10; from 4 to 7 = area 9; (from 7 to 14 = areas 8 and 6). Level 0 corresponds to the foramen caecum, and the measurements of our resections or sections were taken near the midline on the post-operative X-rays (lateral view of the skull). We believe that the possible error of these measurements of lengths is nearly $\frac{1}{2}$ centimeter.

The diagram is divided into three parts, A, B and C. If we leave out for the time being the orbital resections and the lobotomies, it will be seen that in part A nearly all the operations which had no sequelae of a significant post-operative syndrome involved most of area 10 and extended little into area 9. Now, even if one believes firmly in the qualitative theory, there remains the fact that a minimal amount of cerebral resection is necessary for the production of any clinical effect (probably 8 to 10 grammes on each side). It is for this reason that we should discard the five most lateral (area 46) resections in the diagram, as well as the three labelled "small-sized fragments." Even so, there are still 20 selective operations more or less confined to area 10 and belonging to class A.

Part B of the diagram is made up of the patients showing post-operatively the classical hypomanic frontal syndrome. Often these patients break into spontaneous loud singing. There may be some degree of mental confusion, but when vesical and rectal incontinence is observed it is usually due to indifference or even meant as a joke. If we leave out the lobotomies, it will be seen that most of these resections are definitely higher than in class A and probably include much of area 9. These findings, therefore, strongly suggest that the appearance of the prefrontal hypomanic syndrome is related to the suppression of area 9.

Alternative explanations would be :

(a) *A quantitative effect.*—This, it is believed, is not likely; a simple comparison between the lengths of operations A and B shows that there is certainly no prevalence of size on the B side; if anything it would be rather the reverse.

(b) *The pre-operative condition.*—This point needs careful discussion. Firstly it is necessary to limit the comparison to cases submitted to prefrontal operations roughly equivalent in extent. This leaves 20 cases in class A and 18 cases in class B. In A, 14 were classified as intractable pain, and 6 as psychoses; in B, 9 were pain cases and 9 psychoses. Many more cases are, therefore, necessary to draw statistically significant conclusions. The most typical hypomanic syndromes were seen in 4 cases of pain and 2 of psychoses, and it is our impression that the special post-operative syndrome is more closely related to the suppression of area 9 than to the pre-operative personality. Following Petrie's lead on lobotomies (16), our patients were tested pre-operatively and as soon as possible in the post-operative period (Rylander and his associate Mrs. Schalling actually perform tests during the operation itself). We have not yet collected a sufficient number of observations available for statistical analysis, but this line of investigation is likely to yield some useful information both on the role of the pre-operative personality and on the type of post-operative change.

Exceptions.—The first two cases in class B seem to disprove our point.

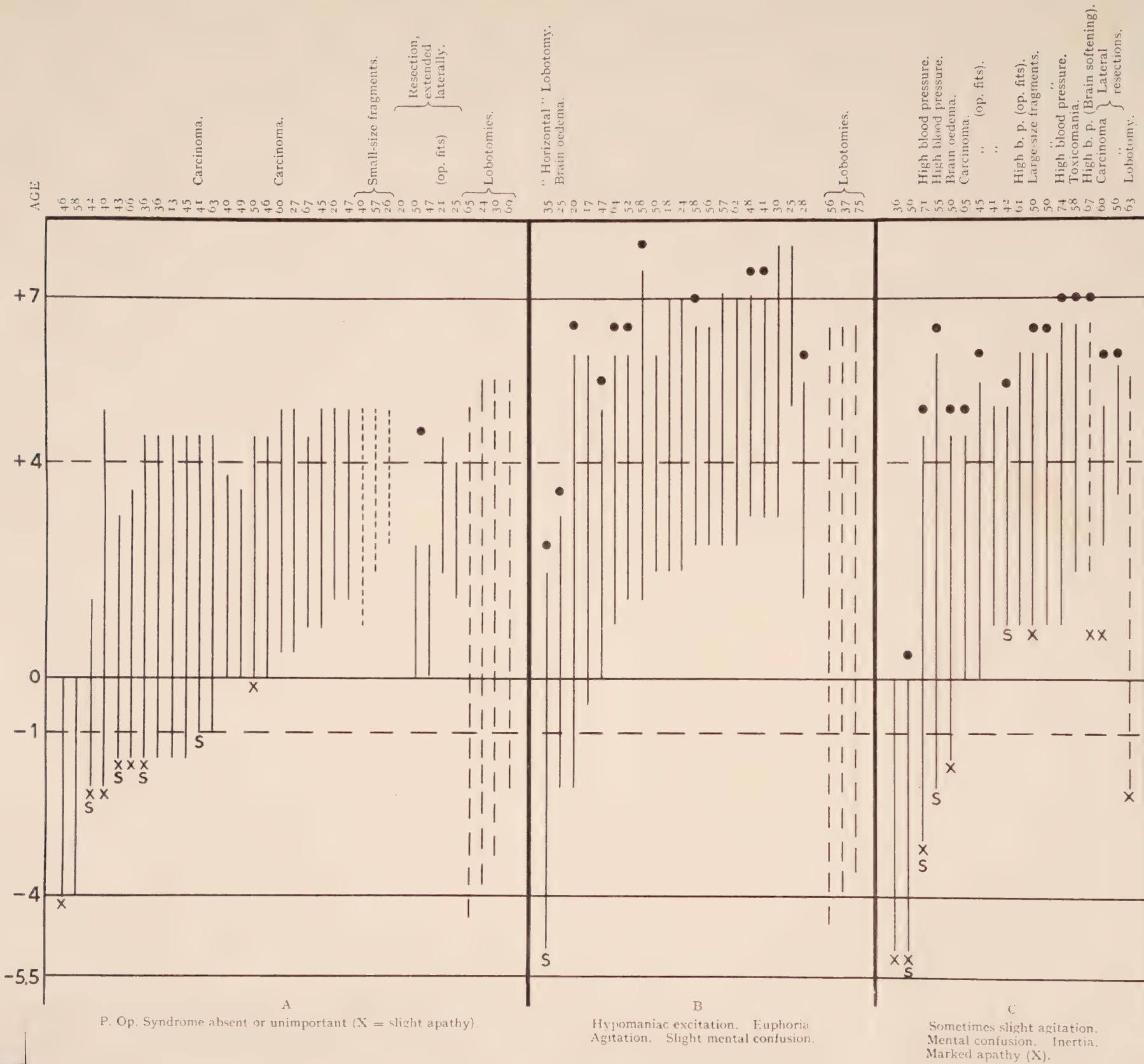


FIG. 1—Post-operative syndromes after prefrontal topectomies (S = Corticle undercutting). (● = Sphincteric disturbances).

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However, the first, though intended to be a cortical undercutting of areas 10 and 11, was in reality (7, Fig. 10) a rather deep section, likely to cut most of the fibres connecting area 9 and thalamus; the hypomanic post-operative syndrome therefore is in accord with the other class B cases. The second case was a topectomy limited to parts of 10 and 11, but was complicated by oedema of the brain developing during the operation.

Part C of the diagram contains a group of patients showing a post-operative syndrome of inertia, apathy and mental confusion; sphincteric incontinence is nearly always present, but seems to be related to the deep, stupor-like disturbance of consciousness. If lobotomies and orbital and lateral resections are omitted, there remains a group of 13 cases. A study of the lengths of incision yields a roughly equal distribution over areas 9 and 10. Furthermore there is no significant quantitative difference in length between class C and classes A and B (except in one case with large-sized fragments). However, in nearly all the C cases there were some general factors which might explain the post-operative changes. More than half of the cases in class C were over 55, against 15 per cent. in class A and 30 per cent. in class B. Moreover, the general condition of the patients should be taken into account: three were carcinomas, one a very deteriorated drug addict, four suffered from hypertension accentuated during operation; of these, two had fits during the night following the operation. Finally one case developed oedema of the brain. We are therefore led to assume that the post-operative syndrome of class C is not directly related to the actual prefrontal removal, but the result of a generalized effect, very likely involving hypothalamic disturbance (7).

In conclusion, this analysis of the convexity operations strongly suggests that *post-operative appearance of the typical hypomanic syndrome has a relation to the removal or the exclusion of area 9.*

Figs. 2 and 3 are taken from especially instructive cases. In Fig. 2 a topectomy of area 10 with no post-operative syndrome (except a very slight apathy) is contrasted with a topectomy of part of 10 and the greater part of 9 with a marked post-operative hypomanic syndrome which began at the end of the resection. In Fig. 3 two successive operations on the same patient are shown: first an undercutting of part of 10 and 9, followed by euphoria, incontinence and mild confusion, all clearing up in a few weeks. As the patient was not relieved of her pain, an undercutting of 10 and part of 11 was performed several months later, with no post-operative disturbance, but a good therapeutic result. This case shows conclusively that the post-operative syndrome cannot be due only to a quantitative factor (a comparison of the two cases of fig. 2 leads to the same conclusion).

2. Orbital Operations.

These may also be discussed with the help of the diagram, Fig. 1: only four resections or sections limited to the orbital region (areas 11, 13, part of 47, area recta anterior and posterior—as described by Beck (1)) were available. Two belong to class A, and two to class C. It is our definite impression that orbital resection tends to produce apathy and incontinence, particularly when it extends slightly on to the mesial side, into “area 12.” In addition we have

five operations involving the convexity and the orbital surface almost equally ; here again apathy seems a predominant feature, slight in A, very marked in C. Lobotomies with orbital involvement are discussed below. As a whole, the orbital post-operative syndrome is less conspicuous than that of the convexity

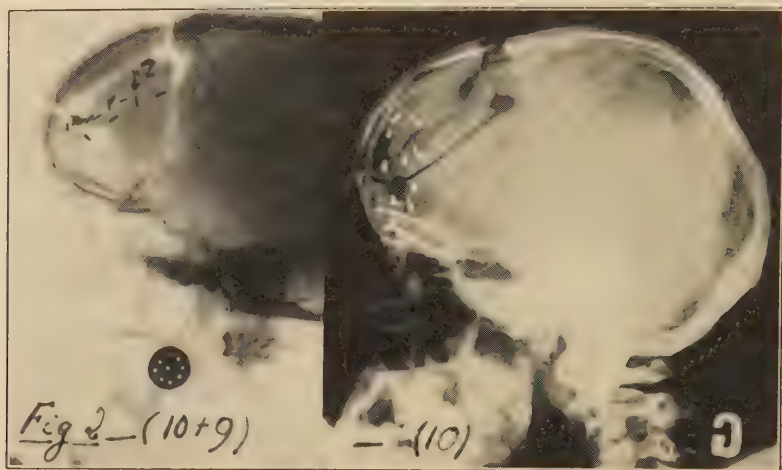


FIG. 2.

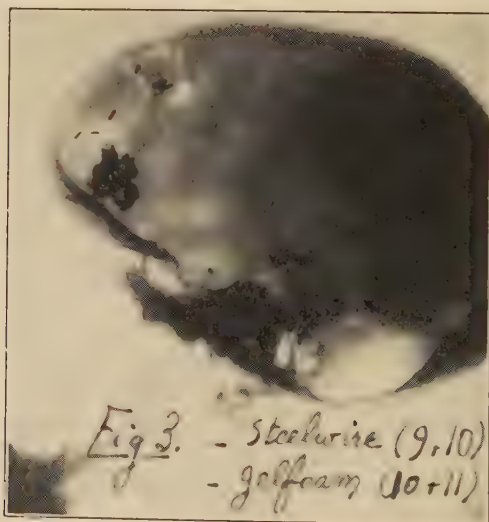


FIG. 3.

but it should be pointed out that the orbital resections did not extend far into area 47. We have never yet observed either restlessness or autonomic disturbances.

3. Lateral Operations.

Five cases of this group belong to class A (Fig. 1), one involving the junction of 8 and 9, two areas 10 and 45 and two areas 10 and 46. In class B we have no case. There were two in class C, but they were carcinomas in a very poor

general condition. Our lobotomies, being as a rule very rostral, spare most of the fibre connections with the lateral prefrontal areas; for this reason they cannot yield much information on the post-operative syndrome, which apparently is not very marked. Here again area 47 was not involved.

4. Mesial Operations.

This group, with 32 patients, is our second largest. Unfortunately it is not yet possible to establish tentative correlations with cortical structures, since there are no precise data on the limits and variations of areas 12, 32, 24 and 25. This uncertainty is particularly true of 32 and 12; area 24 is easier to recognize "macroscopically" since rostrally it envelops the genu of the corpus callosum, which as a rule is a sufficiently clear landmark during operation (9).

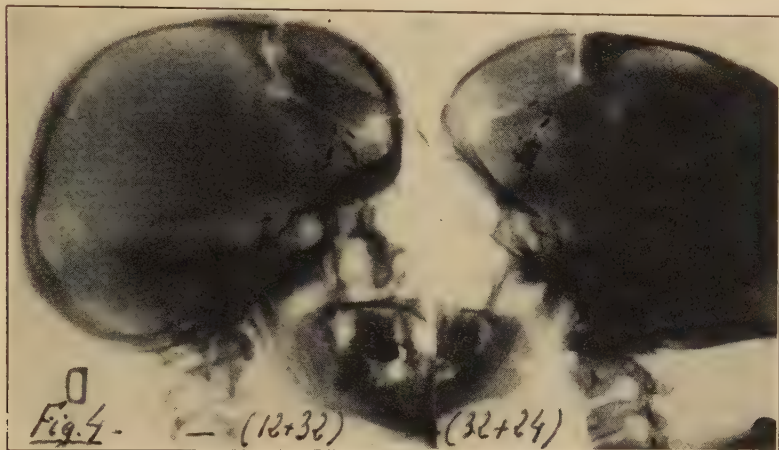


FIG. 4.

For purely practical reasons these cases have been divided into three groups, according to the mean level of the resection above the orbital roof on lateral X-ray view. Generally speaking the length and orientation of these mesial topectomies is about the same: 3 to 4 cm. on each side (1 cm. deep, 2 cm. high), directed obliquely upwards and backwards. *No obvious autonomic disturbances* have so far been observed.

The upper group (roughly corresponding to area 24) is made up of resections centred about 2 to 3 cm. above the orbital roof. We have five such cases (all topectomies), none of which was followed by a clinically significant post-operative syndrome.

The middle group (24 and 32) is centred about 2 cm. above the orbital roof. We have sixteen such cases with only one (cortical undercutting in a patient aet. 65) showing a marked syndrome of apathy, slight confusion, and incontinence. In about four cases there was slight agitation lasting 2-3 days.

In the lower group the operation extends up to 1 cm. above the orbital roof. We have eleven such cases (five topectomies, six undercuttings). In four there was marked apathy, with mental confusion and incontinence of urine

lasting from two to six weeks (ages, 28, 57, 48, 25 respectively; two were topectomies and two undercuttings).

It is therefore suggested that confusion with apathy and incontinence are sequelae most often when cortical destruction extends downwards and forwards on to the mesial prefrontal surface, involving Brodmann's area 12. This indirectly confirms our impression obtained from the few orbital operations of our material, as pointed out above. Fig. 5 demonstrates the two types of mesial resection, with and without post-operative syndrome.

5. *Lobotomies.*

Only eight bilateral lobotomies are available for this paper, all belonging to the anterior or rostral type. They are represented in the diagram of Fig. 1. Three are in class B, all showing a hypomanic syndrome accompanied by



FIG. 5.

urinary incontinence. It is at least suggestive that their upper limit is definitely above that of the four belonging to class A. Only one is in class C with apathy and no incontinence (patient aet. 63).

In Fig. 5, lobotomy with a very typical hypomanic syndrome is contrasted with an apical undercutting with no post-operative syndrome whatsoever (ages 37 and 42 respectively). The main anatomical difference between the two seems to be the exclusion of area 9 in the case of the lobotomy; we believe that this is a corroboration of our findings in the topectomies of areas 10 and 9. In these two cases there is little, if any, difference with regard to orbital involvement, although there must be a difference with regard to lateral extension. However, on the frontal views which are not shown the lateral extension seems the same in both cases. The explanation is that we try to avoid cutting very far laterally in our lobotomies for fear of involving the anterior ascending branches of the Sylvian blood-vessels.

DISCUSSION.

This study of the post-operative syndrome suggests differences of function within the prefrontal region. This, we believe, would have been less clear if

our material had consisted predominantly of complex psychoses, as is the case in the majority of publications on the surgery of mental disease. Most of our material consists of cases of intractable pain and of chronic neuroses. As has been explained previously (9), even if one adheres to a qualitative theory, it is necessary, in order to achieve a good result in a complex psychosis, to remove several areas, which—on the surface—looks like a quantitative effect. In our cases *analysis of therapeutic results* gives additional reasons in support of the qualitative theory of prefrontal activity. They have been published in various papers since 1948 (5, 6, 8, 9). The following is a summary of our results :

I. *Intractable pain :*

Bilateral operations :

Areas 9 and 10 . . .	30	good results	6	doubtful	9	failures
Lobotomies . . .	3	„	„	„	„	„
II-13, 24-32, 45-46 . . .	0	„	„	2	„	5

Unilateral operations :

9-10 . . .	1	„	„	„	4	„
Lobotomies . . .	1	„	„	„	2	„

II. *Agitation and violence (often with epilepsy) :—*

All bilateral :

24-32 . . .	16	good results	„	7	„
9-10 . . .	5	„	„	10	„

III. *Other Psychoses and Neuroses :—*

„	17	good results	„	8	„
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This table calls for some remarks : Group I contains cases ranging from purely organic pain to so-called psychalgias (6). The usual reasons for failure seem to be a resection not extending far enough over both areas 9 and 10, but this should not be interpreted as supporting a quantitative factor (as long as the minimal amount (2×12 grammes) is excised). Some failures cannot be explained by the operation of purely anatomical factors ; the search for psychological factors is imperative (7).

Group II is specially noteworthy for the relationship between generalized epilepsy and behaviour disorders (9) ; when the latter improved or disappeared we often saw a strikingly beneficial effect on the fits, though no cortical focus was found in the electroencephalogram or corticogram of the convexity or the mesiofrontal region (10). Group III is a heterogeneous group in which obsessions and phobias seemed greatly improved by the mesial operation ; in severe psychoses more extensive prefrontal exclusions are often necessary.

The therapeutic results supply some additional data in favour of a qualitative theory although, on the whole, this evidence is less convincing than the

results of the present study of post-operative syndromes. The question arises whether eventually there is a *correlation between ultimate results and immediate syndrome*. So far our material is not in favour of any such correspondence neither in cases of intractable pain nor in schizophrenias. In Figs. 2, 3, 4, 5 all the operations not followed by a significant syndrome finally yielded good results whereas the others were failures, but, of course, the reverse is often also true. For practical reasons, however, the appearance of a hypomanic post-operative syndrome in cases of intractable pain is a good sign, since (if what we propose here is confirmed) it proves the exclusion of a large part of area 9; by cutting down to the level of the foramen caecum or 1 cm. below, most of area 10 is very likely to be excluded: thus, what appears to be the best surgical intervention in intractable pain can be performed with some precision.

The search for selective prefrontal surgery aimed at causing more specific and or less deteriorative changes is a relatively recent one. Cunningham Dax in 1943 started partial lobotomies which he has developed since (4), but for the most part he has dealt with complex psychoses and the anatomical definition of the operations does not appear to be simple. Penfield (15) reported the first gyrectomies: even at that time he emphasized the probable importance of the study of the post-operative syndrome, and went as far as to ascribe psychomotor akinesia with incontinence and severe intellectual disorders to the bilateral removal of the anterior part of areas 6 and 8. Since we never perform a prefrontal operation situated more than 9 cm. above the foramen caecum we have no such cases in our series. Pool (3), who with Mettler originated topectomy, has demonstrated the effect of resection of areas 9, 10 and 46, on "anxiety." More recently, in still unpublished observations, Rylander on patients operated by Sjoquist (17, 18) has studied the immediate post-operative syndrome with great precision, his conclusion being that a convexity undercutting is often followed by a hypomanic syndrome, which is usually absent after orbital undercutting. Scoville, who originated the excellent technique of cortical undercutting, was not in favour of the qualitative theory in his first publications, but recently appears to have observed different personality changes following qualitatively different prefrontal undercuttings: unfortunately so far only an abstract of his paper (19) is available, which deals for the most part with permanent effects. His findings on these changes are more pronounced after a convexity operation than after one on the orbital region. The convexity operation is advised for pain with anxiety (*souffrance* in our terminology (8)): the results of the mesial operation seem to be more promising than judged previously, thus confirming our findings; the orbital operation, of which we have little experience, is advised for relatively mild psychoneuroses.

On the other hand, recent careful psychological work on lobotomies is not in favour of qualitative action (16); the comparison is made, however, between standard and rostral lobotomies. Both these operations are performed along transverse planes, whilst topectomies and undercuttings follow more closely the curvature of the lobe, thus resulting in an entirely different extent of the excluded areas. It is possible that a psychological analysis of this kind applied to our types of selective surgery might yield somewhat different results;

psychological work along these lines is actually in progress, as mentioned above.

Thus it can be seen that the tendency of modern research on the prefrontal lobes is in accord with our present observations. The hypomanic syndrome appears to be related to operations on the convexity and not to interventions on the mesial or the orbital cortex, thus confirming Rylander's findings. We venture to go a little further by attributing it to area 9 rather than to area 10. A possible explanation might be the release of the anterior hypothalamus, the mechanical irritation of which often produces an acute hypomanic syndrome in the course of the removal of a pituitary tumour. In that respect a case of area 10 topectomy with no post-operative syndrome (death from shock on the 11th day after a routine blood transfusion) showed that there were no degenerating efferent fibres from area 10 to the hypothalamus, in contrast to what happens after more posterior lesions in the orbital and dorsal prefrontal regions (Beck, Meyer and Le Beau, in press). Further anatomical work after similar selective operations will be of considerable value for any further physiological analysis of the prefronto-hypothalamic and prefronto-thalamic systems.

As the post-operative syndromes are largely transitory the question of *stimulation rather than exclusion* is raised. Corticography was performed on several of our patients. In all cases but one, areas adjacent to the resected tissues showed, as would be expected, slow waves of the delta type. This does not lend any support for the assumption of possible stimulation of these regions. The one case which showed a very transitory ($\frac{1}{2}$ hour) epileptic focus was a case of generalized epilepsy with behaviour disorder, in whom a small subarachnoid haemorrhage involving area 9 on one side was the site of quickly subsiding spikes and sharp waves. This particular patient had no significant post-operative change after bilateral resection of areas 24 and 32.

Finally one may well ask what kind of light the knowledge of post-operative syndromes casts on mental function. This is mainly a question of theory : firstly one has to correlate, if possible, specific mental changes with the ablation of distinct prefrontal areas ; then to express these changes in measurable variables. At least for the time being, factorial analysis seems to us the most promising method for the selection of psychological elements which in all likelihood will be quite different from the old classifications (5) ; the eventual correlation of such elements to different brain areas would be a definite advance.

CONCLUSIONS.

A study of the immediate post-operative syndromes in 134 patients submitted to selective prefrontal surgery leads to the following conclusions :

(1) A convexity resection (areas 9 and 10) is more often followed by a marked syndrome than an orbital resection (areas 11 and 13), and much more often than a mesial resection (areas 24 and 32).

(2) Resection of area 9 seems to release a hypomanic syndrome, while resection of area 10 usually is not followed by obvious behavioural disturbances.

(3) Perhaps resection of "area 12" is responsible for the appearance of marked apathy with incontinence.

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REFLECTIONS ON ONE HUNDRED CAPITAL CASES SUBMITTED TO ELECTROENCEPHALOGRAPHY.*

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DURING the last eight years the E.E.G.'s of over 100 persons awaiting trial on charges of murder have been examined, at first at Sutton and since 1947 at the Maudsley Hospital. While a few cases were seen during the war, the majority of these prisoners have been examined since the end of hostilities and about 50 of them between 1948-1950. It is difficult to assess to what extent this group constitutes a cross-section of the murderer population. During the four years 1945-48 inclusive some 300 prisoners were committed for trial at Assizes over the whole country on the charge of murder and this is the stage at which the majority of our subjects have been examined.† Some 50 prisoners were examined during this period so that approximately one-sixth of all cases have been seen here. There were no formal criteria of selection, which was usually made by the prison medical officers, but inevitably there has been a greater concentration within the group of individuals suspected of epilepsy or brain disease. Nevertheless, in the last two years the majority of prisoners accused of murder in the London area and home counties have been examined. At the time when the examinations were made, we were supplied in each case with full clinical details and some information regarding the alleged crime by the prison medical officer. By far the largest number of such prisoners has come to us from Brixton Prison. We are greatly indebted to Dr. J. C. Matheson, Dr. Hugh Grierson, Dr. F. H. Taylor, as well as to medical officers of other prisons throughout the country, who have given us all the information available and have collaborated with us in an invaluable way in our investigations.

Stafford-Clark and Taylor (1949) have reviewed the first 64 of these cases and published their findings. These results were presented as evidence before the Royal Commission on Capital Punishment, and the series was then increased to 94 cases by the inclusion of a further 30 examined since Stafford-Clark and

* Based on papers given at the Annual General Meeting of the R.M.P.A. at Leicester, July, 1950.

† Evidence presented before the Royal Commission on Capital Punishment 1-2.

Taylor had made their study of the material. This second group was studied clinically by Dr. Taylor and Dr. Matheson of Brixton Prison. These 94 cases constitute the material which, until now, has been worked up from the clinical point of view as far as it will be possible to do so. However, since then more than a further 15 cases have been added, although the historical data on some of them are not yet complete. While the total number (of prisoners) is now over 110, it is only possible to include 105 of them for most purposes in this paper.

THE CLINICAL HISTORIES.

Only 6 women have been examined. The series includes normal, abnormal and psychopathic personalities, individuals suffering from psychoses, mainly schizophrenic or depressive and a number of mental defectives, epileptics and men suffering from organic states of various kinds. The age range varies from 12 to 59 years but the majority of the crimes were committed by men between the ages of 20 and 30 years (55 cases). Thirteen of the prisoners were under the age of 20 years.

In 37 cases the family histories showed significant morbidity. Of the first degree relatives, in 13 cases suicide or psychosis had occurred; there were 5 cases of epilepsy. Of the fathers of these prisoners, 9 were alcoholic, 1 was epileptic, 3 were insane. While in many cases the early environments were no doubt disturbed, in only 8 cases were the prisoners illegitimate or came from broken homes. Ten had been either in Borstal or Home Office schools. Curiously, the incidence of physical deformities among these murderers was high, being present in 13 cases. There were 2 cases of psoriasis, 2 of deafness (1 using a hearing aid), 4 were lame, 1 had much reduced vision, 1 severe disseminated sclerosis with ataxic gait, and there were cases with amputated fingers, facial palsy and paralysis of an arm from injury.

Assessment of personality is always a difficult matter under the conditions that obtain before a murder trial, owing to the conflicting interests which are evident, but 30 of these prisoners were regarded as having personalities within normal range, 38 others were classified as either abnormal or psychopathic. In 9, previous convictions in the courts were known; 10 had defect of intelligence amounting to borderline mental deficiency. In 15, definite epileptic seizures were known to have occurred, 16 were finally categorized as suffering from depressive or schizophrenic psychoses and 6 from organic cerebral states. This list is an under- rather than over-estimate of the morbid factors in these cases, and it makes a strong case for the view that this group of capital cases is a psychiatrically abnormal population.

TYPE OF CRIME.

In their paper, Stafford Clark and Taylor (1949) divided the prisoners according to the crimes of which they stood charged, into 5 groups, a division which proved very successful. These groups were:

- (1) Killing incidental to the commission of another crime or in self-defence.

- (2) Killing in which a clear motive was apparent or which resulted from violence during the commission of another crime.
- (3) Killing which was apparently motiveless, or in which the motive was very slight.
- (4) Killing with a strong sexual element—a group which included only those in which sexual activities of some kind occurred at the time of murder.
- (5) The killings by insane persons who were either unfit to plead or were found insane at trial or later at a statutory enquiry.

Using this grouping, the further 30 cases already mentioned were added by Dr. Taylor and one of us (D. H.) with Dr. Matheson's help.

Fig. 1 shows the number of cases in each of these groups and the incidence of abnormal E.E.G.s among them.

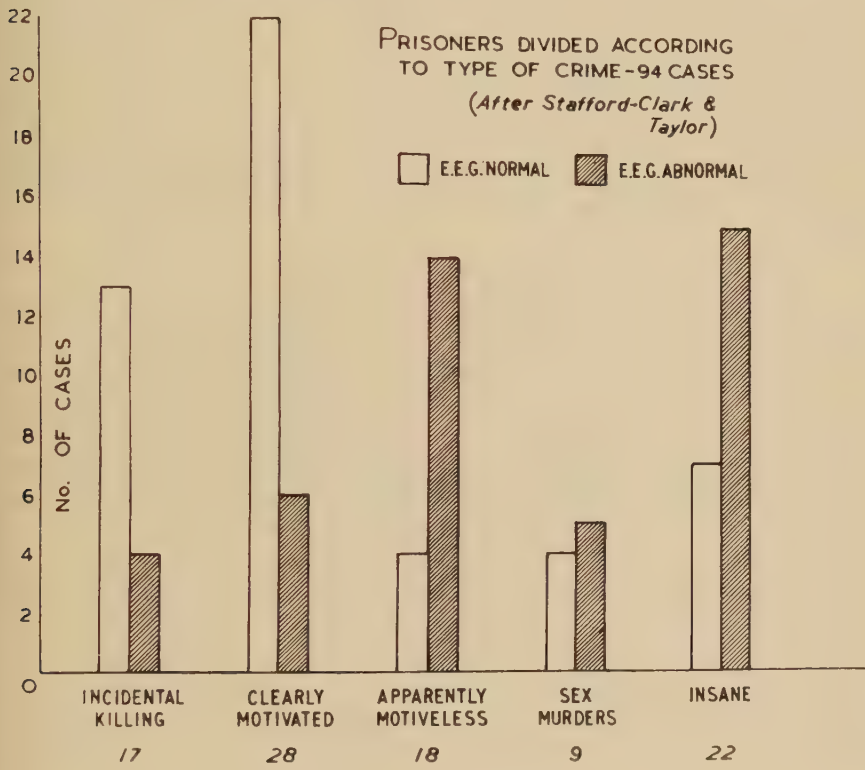


FIG. 1.

These results on the larger series only underline the findings of Stafford-Clark and Taylor. They show, as one would expect, that the "accidental" murders are committed by men among whom there is no greater evidence of E.E.G. abnormality than among the normal population. The "clearly motivated" murders are committed by a group of men among whom the incidence of E.E.G. abnormality is about the same as the neurotic population, or the prison population in America (Silverman, 1943 and Gibbs *et al.*, 1942).

The insane group contains more persons with abnormal E.E.G.s than normal ones and as a group compare probably with the admission ward of a mental hospital. The sex murderers are too small a group to consider, and the most important observation which was made by Stafford-Clark and Taylor, is the very high incidence of abnormal E.E.G.s among Group 3, the prisoners whose crimes were apparently motiveless or with very slight motive. The crimes in many of these cases were indeed remarkable. Eighteen of the 94 murders were in this group. Two were detailed by Stafford-Clark and Taylor. Further examples are :

CASE 3.—A man, aged 22, of low average intelligence was looking after his 2-year-old step-daughter while his wife was out. The child would not stop crying so he picked her up by the heels and swung her round so that her head struck the fire grate. He also kicked and punched her, so that she died of her injuries.

CASE 12.—A soldier, aged 23, of dull intelligence, who had once attempted suicide, had marched 10 miles and was on guard duty one night in 1942. On leaving guard he went to the cook-house and called "Is there any tea, George, lad?" The cook replied, "No—get on your duty." The soldier then swore and fired his rifle at close quarters into the cook's abdomen, killing him. When later the officer asked who fired, the young soldier came forward.

CASE 34.—A young man of 22 had deserted from the R.A.F. He and his wife and baby went to stay in the house of a former mistress. In the presence of his wife he battered in the head of this woman with a hammer while she sat in a chair, and then killed the woman's baby who was crying. The victim had told him not to play the fool with the light switch which he had been turning on and off to irritate her.

THE ELECTROENCEPHALOGRAPHIC FINDINGS.

Of the 105 cases, 55 had normal and 50 abnormal E.E.G.s. The percentage abnormality falls off with age until the age group of 40-year-olds is reached when there is again a slight increase in E.E.G. abnormality (Fig. 2). This type of distribution curve is very similar to the curve for such abnormalities in the psychiatric population, the first and falling part of the curve being that associated, we consider, with those E.E.G. anomalies which reflect a constitutional immaturity of cerebral function. The latter part, when an increase of abnormality is witnessed, we might infer as being related to the advent in patients over 40 of the degenerative cerebral disorders. The clinical states of these prisoners over 40 years of age go some way to support the organic diagnosis. Six of 15 were found insane, only 1 was executed. Five had depression, 4 were chronic alcoholics and there were one each of disseminated sclerosis, mental deficiency with possible sleep paralysis, epilepsy with alcoholism, organic dementia, psychosis (unspecified) and doubtful dementia. Except in the depressive cases and 3 of the alcoholics, all the E.E.G.s were abnormal.

Turning now to the categories and degrees of E.E.G. abnormality, we may classify these, as was done by Stafford-Clark and Taylor (1949) into :

1. "Mild unspecific"—the anomalies found in so many neuro-psychiatric patients, and probably of constitutional origin.
2. The "severe unspecific abnormalities" which may be of constitutional origin, but always raise the doubt of an acquired pathology, and lastly,
3. The focal abnormalities and the epileptic phenomena.

There is little that can be said regarding the first group, the "mild unspecific" abnormality. Between 10 and 15 per cent. of the general population show these patterns and therefore it would perhaps be more proper to call them anomalies rather than abnormalities. Nevertheless, there is a well-established relationship between this type of E.E.G. and general social and psychological insufficiency.

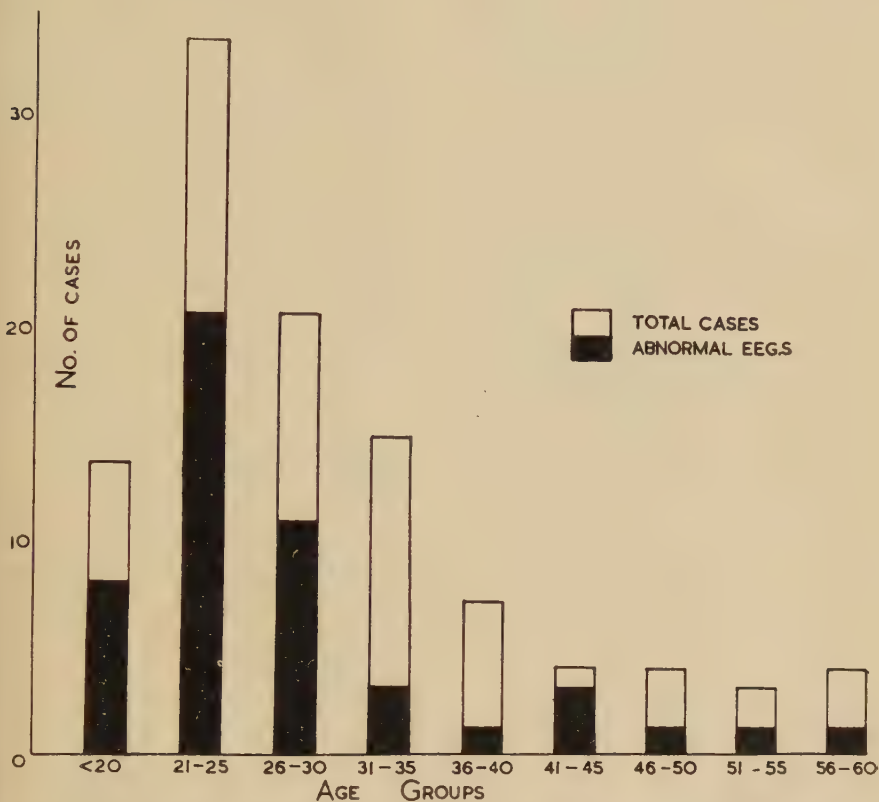


FIG. 2.—Percentage of abnormal E.E.G.s in the 105 cases divided into age groups.

It will be simplest to consider all the cases with severe E.E.G. abnormalities together but to treat the cases showing epileptic activity separately. There are 13 cases with severe E.E.G. abnormalities without any evidence of epileptic activity. These are summarized in Table I. Five of the E.E.G.s contained a focal abnormality suggesting a local pathology; in the remaining 8, the abnormalities were diffuse. Their personal histories and clinical states indicate a great loading of morbidity of all types, 4 were known to have had epileptic seizures at some time. Fig. 3, 4, 5*b* and *c* are illustrations of the type of E.E.G. abnormalities.

What possible significance may be attached to these abnormal E.E.G. findings in relation to the causation of crime? Social custom and the law have long recognized some physiological factors as mitigating the extent to which the person may be said to be personally responsible, e.g., children cannot

TABLE I.—*Severe E.E.G. Abnormality—Diffuse or Focal (Excluding Epileptic E.E.G.s).*

Case No.	Age.	Crime Category.	History.	Crime.	E.E.G.	Result.
12	23	3	Near M.D. Attempted suicide. G.F. suicide	Shot cook in Army with little motive	D	G.Rep.
15	27	3	Alcoholic. Abnormal personality—aggressive, quick tempered	Killed woman who bothered him after drinking	D	Mans.
25	16	3	"Constitutional psychopath"	Killed brother for no apparent reason	D	G.H.M.P.
27	23	3	Two brothers deaf and dumb. Psychopath with sadistic and masochistic perversions	Charged with shooting N.C.O. in his billet	F	N.G.
35	?	5	Epileptic colony 8 years. Acute depression	Strangled wife in bed	D	I.A.
47	22	1	Gross physical disabilities from osteomyelitis. "Immature adolescent"	Killed "accidentally" while committing a robbery	D	Mans.
53	34	2	Two head injuries. Thirteen previous convictions. Two epileptic fits	Murder while committing a robbery	F	G.Ex.
56	29 ♀	3	Head injury and fits as a child. <i>Petit mal</i> seen in prison. Father epileptic	Murdered own child aged 6 and kept body in suitcase for three months	D	?
60	26	5	Schizophrenia. F. insane, M. unstable	Murdered two people without obvious cause	D	G.I.
72	40	5	Organic dementia, ? cause	Murdered girl who was pregnant by him	F	G.I.
82	17	1	Fugues, ? epileptic	Accused of murdering infant	F	N.G.
94	21	3	? Schizophrenia. ? Cerebral disease	Killed his fiancée with very little motive	F	G.Ex.
100	22	3	Two M.D.'s and suicide in family. ? Psychopath	Murdered schoolboy without known motive	D	Mans.

Crime Category.—1 = "Accidental." 2 = Motivated. 3 = Apparently motiveless. 5 = Insane

E.E.G.—D = Diffuse. F = Focal abnormality.

Result.—G.Rep. = Guilty, reprieved. G.Ex. = Guilty, executed. I.A. = Insane on arraignment. G.H.M.P. = Guilty, detained at His Majesty's pleasure. G.I. = Guilty, insane. N.G. = Not guilty. Mans. = Manslaughter.

commit murder or rape, and certifiable mental defect may affect the disposal under certain conditions. Similarly, acts committed in states of physical illness causing confusional states are not held to be liable to the severest penalties.

However, there is no need to discuss here these well-recognized developmental defects and acquired disturbances of the physical basis of mental function. On surveying the 110 capital charge cases, few can be included under this heading. Also crimes committed in episodes of schizophrenic or manic-depressive psychoses will not be discussed, since the mechanisms leading to the crime are in these cases more usefully discussed in psychopathological terms. Exclusion of these groups still leaves some 45 cases where there are abnormal E.E.G. findings or a definite history of epilepsy, whose relationship

to the crime and the criminal remain to be investigated. Of this number 18 are epileptics and the rest show the non-specific "constitutional" E.E.G. anomaly.

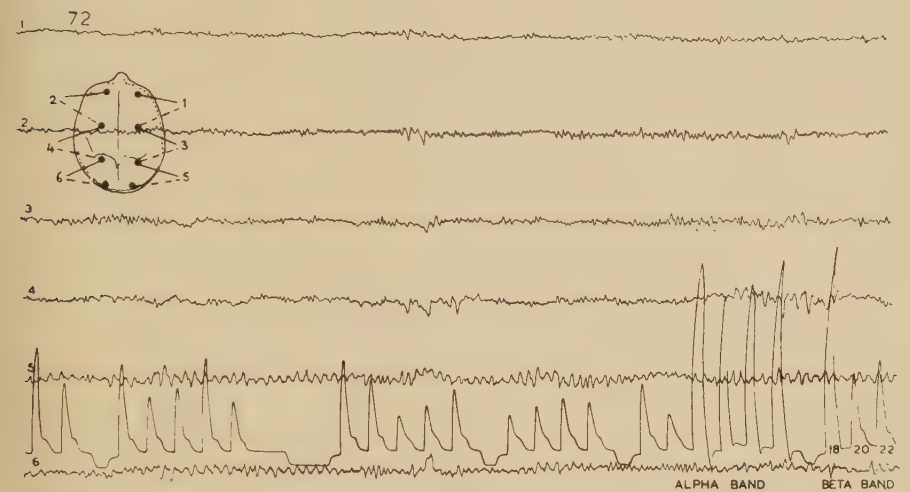


FIG. 3 (Case 72).—A 40-year-old man suffering from an early organic dementia of undetermined cause. Note the presence of irregular sharp and slow waves, especially in the left temporal region (Channel 4).

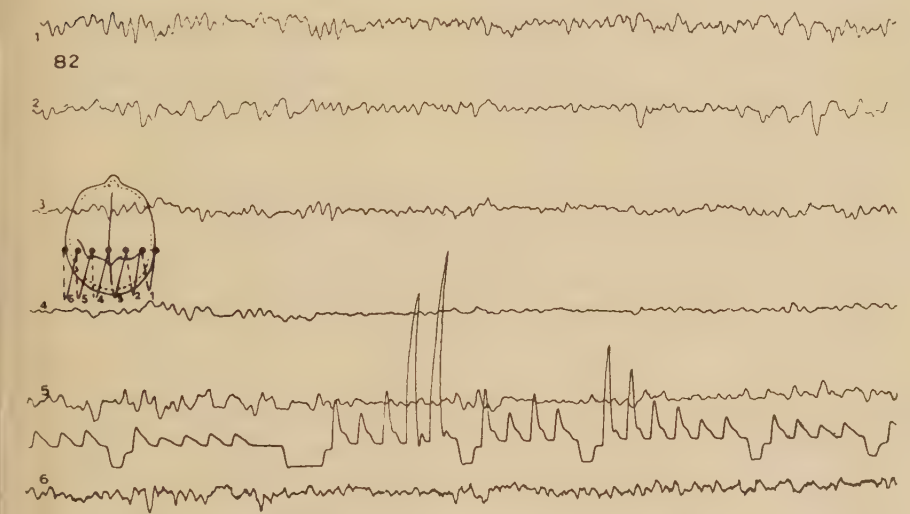


FIG. 4 (Case 82).—A 19-year-old boy with a history of fugue states, possibly post-ictal. Note the focus of 3 1/2 c./sec. activity in the right posterior temporal region.

EPILEPSY.

The relationship to epileptic phenomena is one which is of course of the greatest immediate medico-legal importance. It often happens, as everyone knows, that the defence of epileptic automatism in a hopeless case is offered by Counsel. It is a common happening to find psychiatrists supporting such

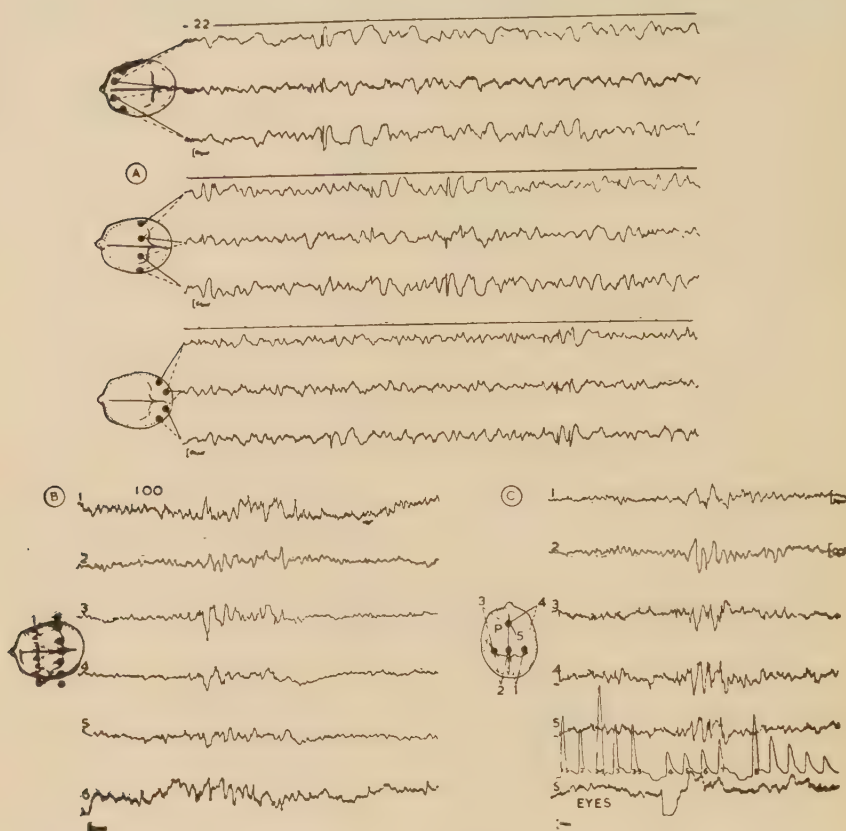


FIG. 5 (a) (Case 22).—A 29-year-old woman who suffered from major seizures for years and showed considerable mental deterioration. Note the bilaterally synchronous spike and wave in all areas and the excess of general slow activity. (Note the paper-speed in this record is slower than in all the others.) (b) and (c) Case 100).—A 22-year-old man with a psychopathic history, who murdered a schoolboy. The records show excess of slow activity which appears to be bilaterally synchronous. (c) is a record taken with a pharyngeal lead (d). (The time scale in this record is as in the other figures.)

a defence with medical evidence, and yet when the accused's statement about his activities at the time of the crime is produced and when all the facts are known, only very rarely is this defence accepted. In the light of these facts and opinions, it is astonishing what a great number among these 110 prisoners either show epileptic activity in their E.E.G.s, or, and this in the present state of knowledge is more important, were known to have had epileptic seizures at some time in their lives. Those cases showing possible epileptic activity have been divided into three groups :

1. Those with specific epileptic E.E.G.s (Table II).
2. Those with no epileptic activity in the E.E.G. but a proven previous history of epileptic seizures (Table III).
3. A history of possible, but not proven, previous epilepsy (Table IV).

There were 9 cases in each of these 3 groups, making 27 in all, of whom 18 could be regarded either on clinical or E.E.G. evidence as being definitely epileptic (Tables II and III).

Five of the first group were chronic epileptics and 3 were known to have personality changes, psychoses or mental deterioration. Two had been in mental hospitals, one as a certified patient (Case 2). Three were not known to have epilepsy, though 1 had a family history of epilepsy and psychoses (Case 22, Fig. 5a). Only 2 were executed.

TABLE II.—*Specific E.E.G. Epileptic Group.*

Case No.	Age.	History.	Crime and Category.	Result.
2	25	Chronic epilepsy with personality disorder. Previously certified patient	Quarrelled with wife over her friends and strangled her. (Cat. 5)	G.I.
5	26	Family state "epileptic fits." Low intelligence. Alcoholic. H.I.	Rape and murder of 69-year-old woman. (Cat. 4)	G.Ex.
11	28	Traumatic epilepsy with psychosis. In M.H.	Deluded about uncle and felled him with flat iron. (Cat. 5)	G.I.
22	29 ♀	Chronic epilepsy. Major seizures for years	Killed her defective child aged 2. (Cat. 3)	Mans.
46	23	Traumatic epilepsy with mental deterioration	Murder and robbery of old man. (Cat. 2)	G.Rep.
48	24	Dull; head injury. F.H. of epilepsy and psychosis	Shot girl-friend's father. (Cat. 5)	G.I.
77	52	Chronic epileptic, low intelligence, alcohol	Strangled mistress after quarrel. (Cat. 3)	G.Rep.
90	23	No known epilepsy. "Black-outs"	Killed both in-laws after birth of his own child. (Cat. 2)	G.Ex.
101	30	No known epilepsy	Stabbed wife. Provocation. Evidence of premeditation. (Cat. ?)	G.Rep.

TABLE III.—*Other Known Cases of Epilepsy.*

Case No.	Age.	History.	E.E.G.	Crime and Category	Result.
13	16	Convulsions in prison. C.P. 1947 as moral defective. Psychopath with perversion	+	Murdered and raped 5-year-old child. (Cat. 4)	G.Rep.
23	32 ♀	Nocturnal epileptic 10 years. Delusions with depression	+	Murdered own children. (Cat. 5)	G.I.
28	27	Neuropathy. Minor epileptic fits. Three members of F. epileptic	+	Murdered sister's child, aged 2. (Cat. 5)	G.I.
35	?	Had been in epileptic colony. Acute depression	++	Killed wife in bed without obvious motive. (Cat. 5)	I.A.
42	34	Fits in Army and in childhood. Aggressive psychopath	-	Killed old man and robbed him. (Cat. 2)	Mans.
45	27	Minor epilepsy. Had a ? fit in prison	-	Murdered doctor. Motive. (Cat. 2)	G.Ex.
54	60	Epilepsy in Army 1915. Discharged. None since 1920. Alcoholism	-	Murdered wife after alcohol. (Cat. 1)	Mans.
56	29	<i>Petit mal</i> . Convulsions before age of 14. <i>Petit mal</i> in prison	++	Killed own child aged 6 after alcohol. (Cat. 3)	? N.G.
82	17	Traumatic epilepsy	++	Murdered infant child. (Cat. 1)	N.G.

TABLE IV.—“Blackouts” and Alleged Epilepsy.

Case No.	Age.	History.	E.E.G.	Crime and Category.	Result
4	40	“Fits” and temper. “Collapses.” Hysteria	—	Stabbed wife in street. (Cat. 2)	G.Ex.
26	35	Defence of epilepsy not accepted. Negative history	—	Rescued children from fire but wife later found dead with wound. (Cat. 1)	Mans.
36	39	“Blackouts”	—	Strangled wife and child after quarrel. (Cat. 3)	G.Ex.
37	24	H.I. aged 10. Violence in attacks after. C.P. 1925. Sex perversion. “Man with glaring eyes”	—	Ran down women with lorry, finally killing one. (Cat. 4)	G.Rep.
49	24	Blackouts in Army	+	Murdered baby aged 7 months. (Cat. 3)	G.Rep.
55	31	Defence of epilepsy not accepted. H.I., alcohol	—	Murdered mistress, her son and daughter. (Sexual character ++.) (Cat. 4)	G.Ex.
67	39	Low intelligence. Alleged fits	—	Murdered elderly woman and set fire to her house. (Cat. 1)	G.Ex.
98	19	Maniacal attacks with amnesia in prison, ? epilepsy. Long history of temper and violence. M. schizophrenic	+	Murdered another youth he disliked. (Cat. 3)	..
108	41	Attacks of nocturnal ? sleep paralysis. Attacks of violence in prison	+	Murdered and attempted to rape young girl. (Cat. 4)	Cert. M.D.

— E.E.G. normal. + E.E.G. abnormal. ++ E.E.G. very abnormal.

In the second group (Table III) 6 of the E.E.G.s were abnormal though not definitely epileptic. It is of interest that 5 of them murdered children and only 1 of the 9 was executed.

In the third group (Table IV), only 3 had abnormal E.E.G.s and 4 were executed (Fig. 6).

The type of epileptic activity in the E.E.G. is worthy of comment. Half of them showed generalized epileptic discharges, all of the “atypical spike and wave” variety and in these cases the prisoners often showed severe depressive or other psychotic symptoms. Five were focal in the inferior part of the temporal lobe and only one focal elsewhere. The types of fits these prisoners had, if they had any, were frequently unusual and not typically epileptic. In only one case was 3 c./sec. spike and wave observed—the age factor may be partly responsible for this.

If we accept the 18 cases as the minimal hard core of epilepsy in our material, this incidence is 32 times the incidence of such phenomena in the general population. This is based on the figure of 0.5 per cent. for epileptics in the population. Even allowing for a large selection of all such cases within the present series from the murder population, the incidence is undoubtedly very great. This evidence is not based on the E.E.G.s alone, for 9 of the 18 cases did not show specific epileptic records, but the histories in these were unequivocal. In fact, only 3 cases out of the 18 were not known to have had epileptic seizures of some sort. The evidence, therefore, for some relationship existing between murder and epilepsy in some murderers is undoubted, but

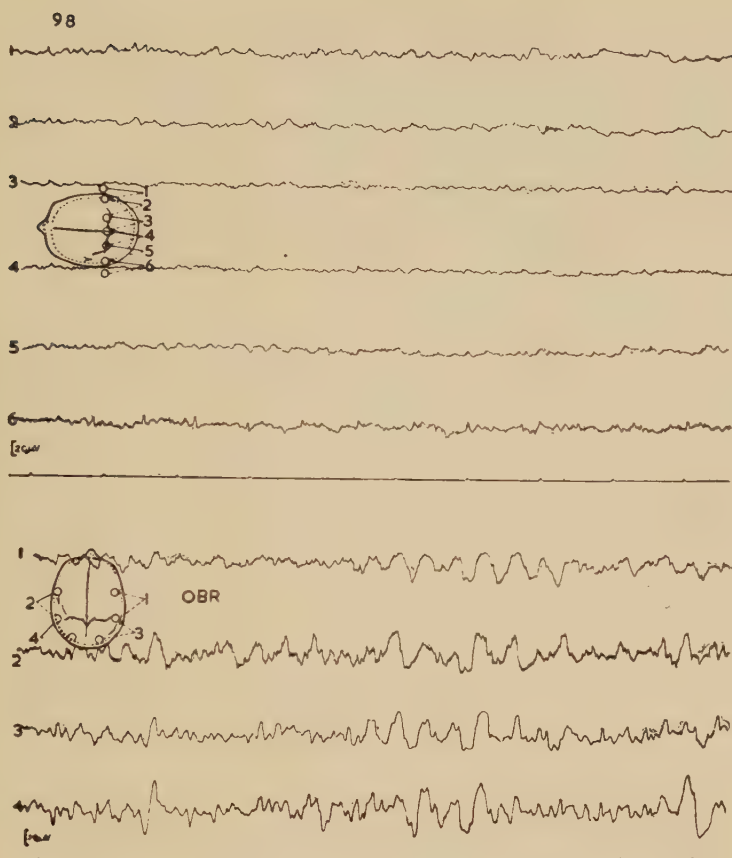


FIG. 6 (Case 98).—A 19-year-old youth who impulsively attacked another youth. Note the excess of mainly 4 c./sec. activity in the central areas (especially channels 2 and 5, which is different from the electrocardiogram best seen in Channel 6). The overbreathing response after 2 minutes when the subject was fasting, is also unstable.

this is not to say that such murders are committed in epileptic seizures or in post-epileptic automatisms.

In those cases which we have had the opportunity to follow in the courts or by a close study of all the depositions and the prisoners' statements, we have not yet observed a case in which we were not at the end satisfied personally that the chances of an epileptic seizure preceding the murder were extremely remote. In some cases, the accounts of witnesses, the time factors surrounding the murder, and the prisoner's behaviour immediately following his crime, made it as certain as it was possible to be that no seizure had occurred. This opinion, which has only been reached with difficulty, is, of course, in conformity with the established view of forensic experts and notably that of Sir Norwood East, that murders are only rarely committed in or after epileptic seizures. As a matter of fact, violent or dangerous behaviour is rarely seen during epileptic or post-epileptic automatisms in any patients. This would appear to be a generally held view based on clinical experience. It has

certainly been our own experience from an active epileptic clinic and from a ward devoted to the problems of epileptic behaviour. Dr. Denis Kennedy has assured us that at Lingfield Epileptic Colony dangerous behaviour after fits is almost unknown. Marchand and Ajuriaguerra (1948) amongst many others remark that, for example, the behaviour in a post-epileptic automatism is only occasionally violent. In support of this is the evidence from another direction that children referred to us for temper tantrums as being possible epileptic equivalents rarely show any E.E.G. changes suggestive of epilepsy, though the records are often abnormal.

Because of the forensic importance of the subject it is important to know under what conditions dangerous behaviour is witnessed in relation to epileptic fits. Such behaviour, if it is to include a spontaneous assault or murder, must be purposive, co-ordinated and sustained. Now it is obvious that no such behaviour is possible during the cortical discharge which accompanies a generalized major seizure, nor during a true *petit mal*, which is the wave and spike seizure. In the latter case full recovery of consciousness is immediate and there is no period of automatism. The major seizure is followed by a shorter or longer period of mental confusion which gradually lightens or passes into sleep. During some stage of this recovery process during which there is great disorganization of the electrical activity of the cortex, the type of behaviour in which murder could be committed is certainly possible and no doubt some murders have occurred under these circumstances. But in the 18 cases of the present series the facts surrounding the crimes excluded the occurrences of major convulsions beforehand with a high degree of probability in the majority. Nearly always the prisoners could recall events right up to the moment of the assault. The amnesia for the crime was variable but upon this in some cases, little confidence could be placed.

Post-ictal confusional states also occur after the peculiar types of seizure known as psychomotor attacks, automatism, etc. This type of seizure is one usually held to have occurred when antisocial behaviour happens in an epileptic, because in some types there is a partial hold on consciousness during the actual cerebral epileptic discharge. In the dozen or so such cases in which one of us has been able to record E.E.G.s (Hill, 1949), there was slow activity on one side. This was accompanied during the seizure by semi-purposive movements such as fumbling, chewing, etc. Never was behaviour sufficiently co-ordinated on a large enough scale to constitute an aggressive threat. On the whole, therefore, it is not possible to relate narrowly the aggressive acts of epileptics to their actual fits, but there must be instead some more general relationship.

In discussing the role of epilepsy in this connection it is advisable for the sake of clarity to adhere strictly to Hughlings Jackson's definition of the epileptic discharge as a sudden excessive discharge of the grey matter, the clinical aspect of which is the fit, and the E.E.G. equivalent the spike. It is necessary to keep this definition clearly in mind, as in any one patient suffering from such sudden excessive discharges there are often other abnormal physiological and psychological phenomena, apparently unrelated to fits, e.g., personality disorders and speech disturbances, and episodes of disturbed behaviour of

varied character such as somnambulism, fugues, maniacal outbursts, catatonic episodes, depersonalization, etc.

The E.E.G. changes in the prisoners do not differ in type from the range found in the epileptic clinic, in which is seen a considerable proportion of cases with behaviour disorders. The absence of classical 3 c./sec. spike and wave is of course due in part to the age factor, but it also accords with our experience that such cases do show only mild behaviour disorders and these only when there is an obvious psychogenic element in the total situation. *Grand mal* seizures tend to be associated with abnormal mental states, e.g., the so-called "epileptic personality." Psychomotor attacks are more commonly associated with behaviour disorders than any other type of epilepsy, e.g., Gibbs, Gibbs and Fuster (1948). In these last cases one common factor between the fit and the behaviour disorder is probably the location of the epileptic focus in the temporal lobe as we have shown that even non-epileptic foci in the temporal lobe are associated with behaviour disorders (Rey, Pond and Evans, 1949). A possible reason is that this area appears to be, with the orbital frontal cortex, a centre of cortical representation of autonomic functions. Kaada and others (1949) have recorded variations in blood pressure and respiratory rate from stimulation of the temporal pole in monkeys, and Chapman (1950) and others have made similar observations in man at operation. Post-encephalitic behaviour disorders have long been suspected to be related to interference with the lower hypothalamic vegetative centres. The temporal-orbital areas represent still higher levels of representation of autonomic function and it is possible that the temporal foci seen in some of these epileptic cases cause autonomic disturbances by discharge at this higher level.

There are still several types of episodic behaviour disorder which it is difficult to include under any of these categories. As an example may be quoted an epileptic who suffers from periods of several days' length of depersonalization and derealization. There is no gross change in his record before, during and after such episodes.

On the other hand, Figs. 7 and 8 are of a patient who suffered from recurrent catatonic episodes, followed usually by one or two major seizures. He admittedly shows cyclic E.E.G. changes but not of the sort that could be ascribed to post-ictal states or to recurrent temporal lobe discharges. Such patients tempt one to consider that there are some more general cyclic biochemical or physiological changes. An epileptic fit is not a disease but a train of physiological events which can be set in motion in "normal" brains given sufficient provocation. It is well known that the factors of blood sugar, pH, etc., alter the fit threshold and there is some evidence that the homeostatic mechanisms in epilepsy are less efficient than normal. Lennox and Cobb (1928) in their classical review of epilepsy show how variations from day to day of biochemical factors parallel the number of epileptic seizures. The numerous studies of blood chemistry in epilepsy usually show values within the normal range but a wider variation than usual from time to time in the same person.

Occasionally it is apparent that the abnormal behaviour is not related to epilepsy directly but both depend on a common factor of brain damage. For

example, the post-traumatic epileptic may have a hemiplegic disorder and a speech disorder. In such cases the behaviour can be explained without reference to epilepsy, as Barbeau (1944) points out. However, it is noteworthy that no case of traumatic deterioration without epilepsy and only one case of non-traumatic dementia without epilepsy occurs in this series.

The mechanisms described so far may act in releasing abnormal behaviour but there is no evidence that the type of behaviour released can be simply

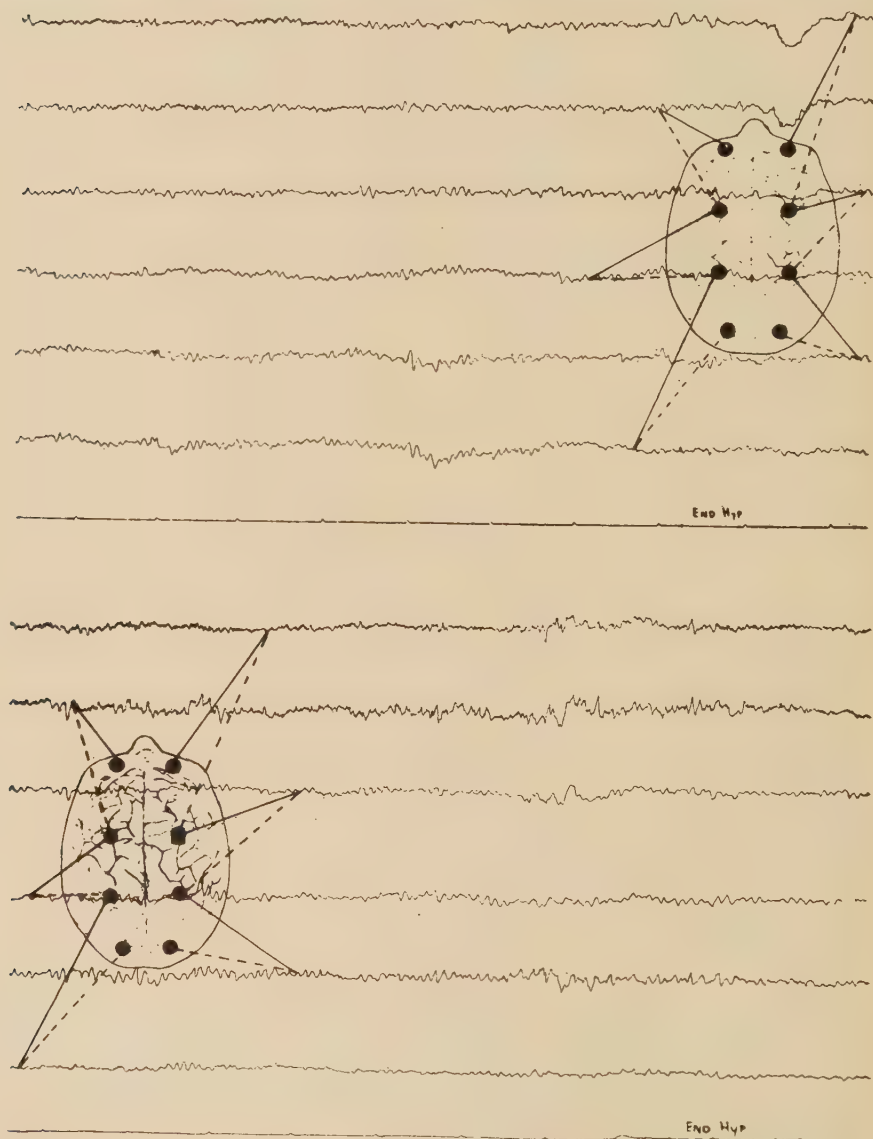


FIG. 7.—Records taken at the end of three-minute hyperventilation in a man before and during a catatonic episode. The records were taken fasting at the same time of the day. Note the greater instability in the second record while the patient was well.

explained on the basis of these release mechanisms. It has already been pointed out that there appears to be no evidence connecting epilepsy as such and aggression, so that other possible causes for this trait must be looked for. In the case of aggressive behaviour in psychopaths generally, one of us, Hill (1947) has demonstrated the improvement produced by benzedrine which they will tolerate in large doses—50 mgm. a day or more; and it was argued by analogy with the effect of benzedrine in reducing appetite and hunger that

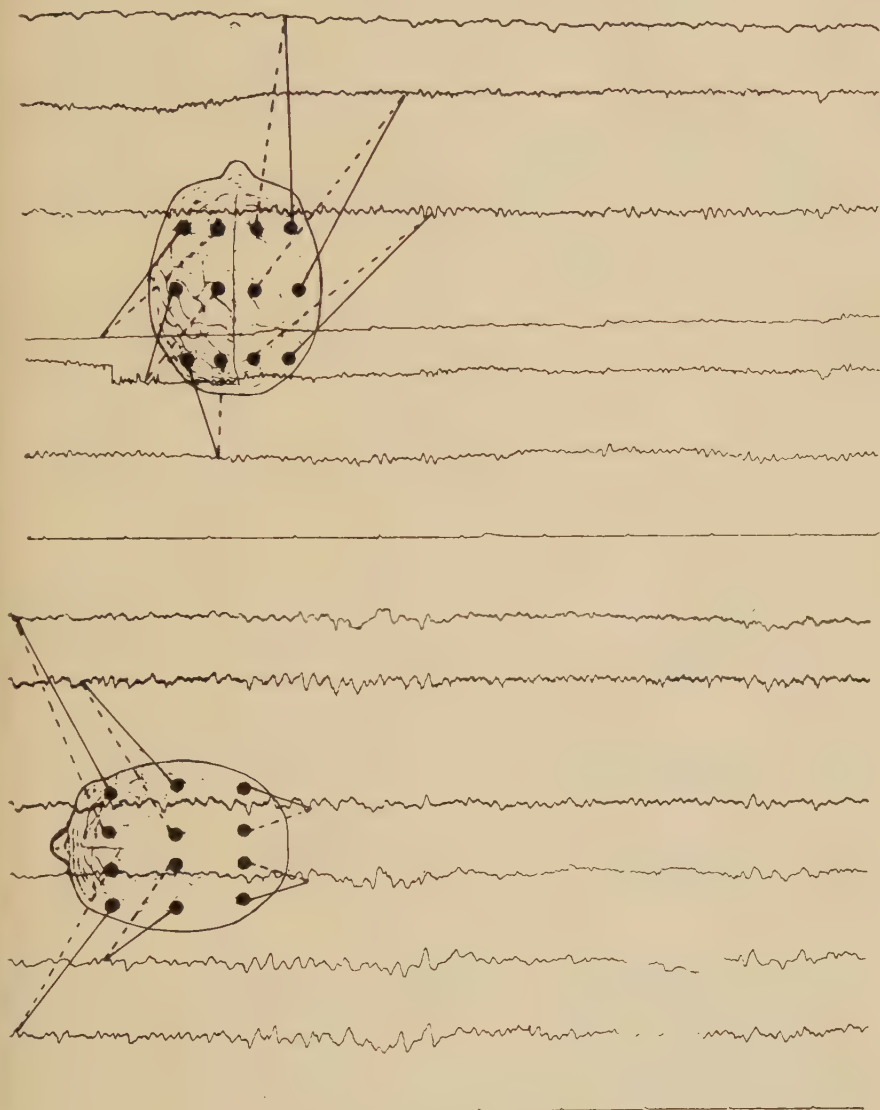


FIG. 8.—Records of the same patient as Fig. 7. Hypoglycaemia has been induced by intravenous insulin and the blood-sugar values at the time of the two sections of the record are 45 and 47 mgm. per cent. respectively. Note the much greater abnormality in the lower record taken while the patient was well, compared with the upper one done when he was in catatonic stupor.

similarly the aggressive drive is cut down to manageable limits. It is equally possible to argue that it acts by increasing cortical control of some more primitive and basal centre of impulsivity. In support of the latter is the fact that benzedrine in children often has a very marked quietening effect, even leading in some cases to sleep.

PHYSIOLOGICAL CONDITIONS AT TIME OF CRIME.

The crimes of 16 of the cases were committed under conditions of alcoholic intoxication, severe fatigue or starvation, e.g., Cases 12 and 15 (Table I), cases 2 and 5 (Table II), Case 54 (Table III). Eleven of these had abnormal E.E.G.'s, even when taken under "normal" conditions, half of them epileptic in character. This is a significantly greater proportion of abnormal E.E.G.'s than in cases not committed under physiological stress. Further changes may often be induced if the physiological conditions at the time of the crime are simulated by, e.g., starvation, hydration, etc.

An early case of the influence of physiological factors inducing abnormal E.E.G. findings and mental changes is that reported by Hill, Sargant and Heppenstall (1943). In this case the murder was committed in a state of partial starvation and after 4 pints of mild beer. Simulating these conditions it was possible to show that the accused's previous mildly abnormal E.E.G. was grossly abnormal and that overbreathing such as would have been induced by the quarrel preceding the murder would have produced a slight but definite impairment of consciousness.

The following is the history of a patient recently under our care :

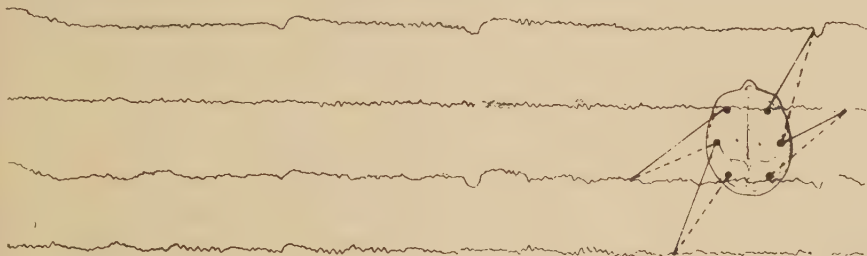
He was a young man, the only son of a professional man, whose history of maladjustment appeared to date from his Army service as a conscript. After several minor offences and a court martial for assaulting a corporal he was invalided out with a diagnosis of psychopathic personality. A few months ago he was brought up to London by his father on business, stayed behind and after a day without food he began to drink, consuming in all several cocktails and about 6 pints of beer. He then aimlessly took a tube to Hampstead and suddenly attempted to break into a doctor's house. When the police arrived he struggled violently but he has no recollection of the events until he was in the Police Station later on. Professor Cloake, to whom the case was referred, has kindly allowed us to use the E.E.G.s (Fig. 9) which were taken under standard conditions and after simulating the conditions under which the crime was committed. There is a marked difference in the dominant frequency which is slowed from the alpha to the theta range after hydration.

The type of E.E.G. changes seen cannot be ascribed to a permanent effect of the alcohol or starvation, etc., for various reasons, e.g., the type of changes are not those seen in acute or chronic intoxication but are those often found in psychopaths and epileptics without any history of alcohol. Rather it is that the abnormal E.E.G. already is a factor of disturbed cerebral functioning which is potentiated by the second factor of alcohol.

Leaving aside for the moment the cases with a history of epilepsy or with epileptic E.E.G.s we find that the E.E.G. changes found are of the type commonly seen in psychopaths. At the present these slow wave abnormalities are best regarded as evidence of constitutional immaturity of cerebral function.

There is some evidence that this relatively non-specific finding occurs in a small percentage of the general population, the percentage falling as the group tested is more and more one selected for physical and mental efficiency. It is low, for example, in Air Force pilots (Williams, 1941). Furthermore, there is evidence that persons with such unstable E.E.G.s show an increased tendency to unstable overbreathing responses, and an increased tendency to the appearance of slow rhythms with lowering of blood sugar by insulin (Heppenstall, 1944). As a group, therefore, persons with such E.E.G.s tend to be vulnerable physiologically and psychologically.

Before beer.



After beer.

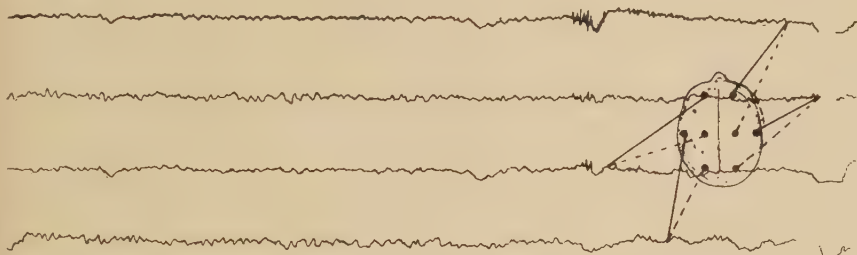


FIG. 9.—Records of a 19-year-old man under standardized conditions and after the ingestion of four pints of beer. Note the slowing of the dominant frequency after hydration. (Records taken by Professor Cloake and reproduced by his kind permission.)

Even before electroencephalography the role of temporary changes in the physiological conditions of the brain in precipitating mental abnormalities and disturbances in behaviour was well recognized. "The hungry man is an angry man" runs an old adage. The literature on peculiar disturbances in behaviour with insulin-induced hypoglycaemic reactions in diabetics has been summarized and discussed by Wilder (1947). A wide variety of actions can occur; only occasionally are they aggressive in character. During the war the mental oddities of pilots exposed to low oxygen tensions at high altitudes were well recognized. Fatigue and sleepiness have also been the subject of investigations, e.g., by Kleitman (1939). The effects of alcohol are, of course, universally recognized, and they may be for the meantime included under this heading because of the many similarities induced by the reversible intoxicating action

of this drug and the temporary disturbances of homeostasis induced by starvation, fatigue, hypoglycaemia, etc., both in the clinical picture and in the E.E.G.

In an interesting review from a hospital for the criminal insane of Quebec, Barbeau (1944) reports that 1.6 per cent. of all admissions over a period of 20 years were epileptics—34 cases. He points out that in many of the cases the actual crime was purely nominal and that there appeared to be no particular type of crime associated with epilepsy. Within this group there was a high percentage of cases with psychological disorder or brain injury and many of the crimes committed or attempted were done under the influence of alcohol. In a study published after this paper was first given, Alström (1950) notes how many of the acts of violence committed by epileptics occur under the influence of alcohol. Four of the 18 definite epileptics in our series were under abnormal physiological stress at the time of the crime.

PSYCHOLOGICAL FACTORS.

From the preceding discussion it would not be too conservative to say that physiological investigations have not so far provided us with definite causes for the aggressive character of the acts committed by murderers, though they have perhaps helped to understand how it is that crude violence can be released in susceptible subjects. We must therefore consider what light may be thrown on aggression by psychological studies. As far as the prisoners are concerned, it is obvious that detailed psychological and social studies are out of the question while the prisoner is in prison awaiting trial. Nevertheless, the Prison Medical Officers have usually supplied us with much relevant information. Dr. Taylor and Dr. Stafford-Clark have kindly allowed us access to some of their notes and from these it is noteworthy that 5 out of 14 epileptics were aggressive subjects as were 8 out of 30 who had constitutional non-specific abnormalities. This proportion, high as it is, compared with epileptics as a group, would undoubtedly have been higher were more details available.

This aspect of the Borderland of Epilepsy has long been clinically recognized. Bratz (1911) for example, as is well known, started a long controversy with his attempted delineation of *Affekt Epilepsie* as a distinct group (see Guttman, 1929). There were attempts to describe the effect of emotion or affect as due to a roundabout mechanism of overbreathing producing tetany and so a convulsion. An alternative explanation was that such patients (whose abnormal personality traits were well recognized) had labile vasomotor control—another aspect of disturbed homeostasis which predisposes to fits. These ideas have been generally discarded, since the E.E.G. suggests quite other mechanisms. From present-day knowledge of the cortical representation of autonomic function a more direct relation between emotion and autonomic discharge may be assumed which involves the interaction of cortex and basal areas directly without the mediation of any vascular or biochemical effect. Whether an epileptic fit in the sense of a sudden excessive discharge of the grey matter is then produced, depends on still further factors, which may be either local, in the sense of an epileptogenic scar, or general, as in the case of so-called

idiopathic epilepsy, where the lowered threshold to discharge is shown by, e.g., the leptazol threshold.

We have had occasion to examine carefully a number of epileptics and have obtained some idea of the relation between personality and the character of the fit and actions performed during and after it. In all cases where aggression was a prominent feature it was psychologically comprehensible. Recently we had as a patient a probationer nurse who made one attempt at suffocating a newborn baby with a deformed jaw. Later on she attempted to strangle a nurse. Both attempts seemed to be quite senseless and unpremeditated, and apparently out of keeping with her previous personality. Her E.E.G. showed a marked excess of slow activity, and spikes and waves were induced with a small dose of leptazol given in divided doses by a standardized technique. On further investigation of her psychological state she gradually revealed that beneath her apparent normal façade were a wealth of aggressive fantasies and dreams, so that the incongruous aggressive acts were shown to have a comprehensible psychological relationship with her personality.

The part played by the temporal lobe may be again relevant. It has already been mentioned that we have observed many psychological factors which appear related to temporal lobe disorders. Penfield has shown that electrical stimulation of the temporal lobe can cause past experiences and memories to be revived. Associations peculiar to the individual appear to become here part of the person's "physiological" structure.

The differences between epileptic and non-epileptic abnormalities may not therefore be as great as it appears, from two points of view. Firstly, there may be common physiological release mechanisms such as increased tendency to disturbances of homeostasis and cortical control. Secondly, there is no evidence that aggression has any peculiar relation to epilepsy.

THE VICTIMS.

Reflections upon these 110 prisoners should not omit the victims. A study of the types of victim revealed one interesting point. 66 women, 26 men and 17 children were murdered. The high incidence of women victims depends, perhaps, upon the fact that over 90 per cent. of the murderers were men. There were 27 wives, 11 mistresses, 13 girl friends, 2 mothers and 13 other women of all ages. Child murder is always an interesting psychological phenomenon. The three groups of epileptic or alleged epileptic murderers—that is, 27 individuals—killed 8 children, whereas the remaining 83 non-epileptic murderers killed only 9 children. This relationship between child murder and the epileptic disorders is statistically significant, but its meaning is quite obscure. Obviously this may be a psychopathological, not a physiological problem.

LEGAL FATE OF THE PRISONERS.

In conclusion, brief reference should be made to Society's attitude to these prisoners. This attitude, which is very properly expressed by the Judges, juries and by the firmness with which prosecution prosecutes its case, determines to a much greater extent than the wording of the McNaghten Rules, what in

the end is the fate of any given man accused of the most serious of all crimes. It is a familiar experience to see the McNaghten Rules ignored, or their meaning stretched suitably to accommodate this attitude towards the accused. How is this contemporary attitude expressed by the figures in the present series? Age and the type of crime are the most important general factors. Stafford-Clark and Taylor's paper shows that Society's attitude to murders involving sexual offences such as rape, is quite clear. Six out of 9 of these prisoners were executed, by far the highest percentage executed in any group. In contrast, the group of prisoners whose crimes were apparently motiveless called out a different attitude towards them. It will be recalled that these prisoners showed a remarkably high incidence of unexplained E.E.G. abnormality. Of 18 cases only 2 were executed. In 5 cases the prosecution reduced the charges during the trials to manslaughter. In 4 cases the prisoners were reprieved after being condemned to death. One man only was found insane at trial. Two were found "not guilty." Society is very unwilling to hang such persons.

As far as age is concerned, Fig. 10 tempts a speculation and perhaps a pious hope which has been fostered by a psychiatric attitude to crime, but

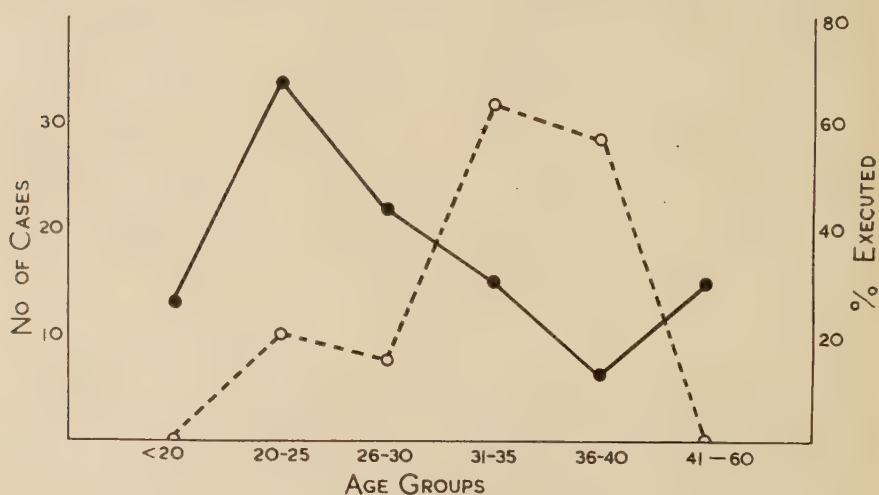


FIG. 10.—Distribution by age of total number of prisoners (black line) and of the percentages that were executed (dotted line).

one which is perhaps not generally held by psychiatrists. The majority of murders in this series are committed by young men under 30 years of age. Not many of these are executed. By law, no murderer under the age of 18 at the time of the offence is executed, and in fact none of this series under the age of 20 years was executed and only 20 per cent. of those aged between 20 and 30. Over 30 the percentage rises sharply to 60 per cent., to fall again over the age of 40 years. These figures contrast strongly with the analysis by age of all males convicted of murder which was presented as evidence by the Prison Commissioners to the Royal Commission on Capital Punishment. According to this series, which covers the period 1900-48, the percentage

executed has been between 50 and 60 per cent. over the age range 20 to 60 years. The discrepancy between the total number and our series, may be because there is in fact a tacit recognition, not openly expressed, of immaturity factors in our series which diminish culpability of the prisoners and of which the abnormal E.E.G. may be one expression. Similarly, so few murderers over 40 in this series are executed, perhaps because there is again a tacit recognition of factors causing deterioration of personality and thereby of culpability. If this be so, we may perhaps look forward with confidence to the time when knowledge of those factors, psychological and physical, will surely extend the range of our understanding of immaturity on the one hand and degeneration on the other and the gap will close.

SUMMARY.

One hundred and five capital cases submitted to electro-encephalography before trial are reviewed in the light of what was known of their past histories, personalities and the circumstances of the crime. Only 6 were women. Eighteen cases were definitely epileptics. Thirty-eight had abnormal personalities and 37 a family history of mental disorder. Just over half showed abnormal E.E.G.s, the percentage falling with age up to the age of 40. In 16 the crime was committed under the influence of alcohol or other physiological stress.

As indicated in the text, we are much indebted to the medical staff of Brixton and other prisons, and particularly to Dr. J. C. Matheson. It is also a pleasure to record our gratitude to the Prison Commissioners who have granted permission to publish this work although it does not necessarily represent their views, and to Professor Cloake for kindly allowing us to see his records. Fig. 1 has already been published in evidence given before the Royal Commission on Capital Punishment.

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A THEORY OF E.C.T. ACTION AND ITS BEARING ON THE BIOLOGICAL SIGNIFICANCE OF EPILEPSY.*

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THE starting-point of the line of thought to be pursued here was some work reported in detail elsewhere† (Roth, 1951), on the changes in the electrical activity of the brain produced by electro-convulsive therapy. When the findings were related to the known clinical and physiological effects of E.C.T. three converging lines of evidence could be discerned :

(1) *The Changes in the Electrical Activity of the Brain Produced by E.C.T. and their Significance.*

Many workers have observed that there is little or no correlation between the process of recovery during convulsive treatment and the slow wave changes the latter commonly produces in the E.E.G. (Moriarty and Siemens, 1947 ; Weil and Brinegar, 1947). The patient may show symptomatic improvement or get quite well long before any change is registered in his E.E.G. After prolonged or intensive treatment the E.E.G. shows a qualitative transformation more striking and sustained than that to be demonstrated by any other physiological test in man. The change has certain characteristic features often encountered in electro-encephalography, consisting of highly rhythmic delta waves synchronous in the two hemispheres and most prominent in the frontal regions. It has long been suspected that such E.E.G. patterns and the spike and wave rhythm in particular had a diencephalic origin (Gibbs, Lennox and Gibbs, 1936), for they may commence in widespread areas of both hemispheres simultaneously and their termination likewise occurs in a synchronous and symmetrical manner on the two sides, nor are these features altered by section of the corpus callosum. The theory of a subcortical source for such E.E.G. patterns has recently been strengthened by the work of Jasper and his associates (Jasper and Fortuyn, 1946 ; Hunter and Jasper, 1949 ; Jasper, 1949). As there were already a number of observations on record to suggest that some of the effects of E.C.T. were due to an action on the diencephalon (Gellhorn, 1943, 1949 ; Delay, 1946 ; Van Harreveld, 1947), we investigated the possibility that the E.E.G. changes also had a diencephalic origin.

Serial E.E.G. examinations were carried out under light thiopentone anaesthesia in forty-five patients. The majority of the patients were studied regularly before, during and after E.C.T. This method of investigation was

* A brief version of this paper was communicated to the Annual General Meeting of the R.M.P.A. at Dumfries.

† To be published shortly in the *Journal of Electroencephalography and Clinical Neurophysiology*. An essay embodying this report, together with some of the material in the present paper, was awarded the Burlingame Prize for 1951.

chosen because barbiturates are generally held to owe their sleep-producing properties to an action on the upper mid-brain. The evidence for this comes from experimental pharmacology (Pick, 1927; Keeser and Keeser, 1928), clinical neurology and the work of Bremer (1935, 1937) on the "cerveau isolé." Evidence has recently appeared, moreover, (Moruzzi and Magoun, 1949; Lindsley, Bowden and Magoun, 1949) to suggest that this action releases from inhibition the diencephalic source of rhythmic bilaterally synchronous slow discharges. Latent changes in the electrical activity of the brain due to an influence by E.C.T. on diencephalic structures might, therefore (it was reasoned) be evoked by barbiturate anaesthesia.

The findings, which are to be described in detail elsewhere, may be summarized as follows:

(a) The thiopentone E.E.G. showed a transformation from an early stage of treatment when the routine record was in the majority of cases unchanged. The typical change was fully developed in most cases after the third treatment, and not seen in pre-E.C.T. thiopentone records. It consisted of a highly rhythmic discharge of 2-3 per second slow waves predominant in the frontal regions, bilaterally synchronous and with a distinctly paroxysmal character (Fig. 1). Its duration gradually increased with the progress of treatment to a maximum of 150-200 seconds after 7-9 convulsions. The appearance of these changes preceded or approximately coincided with the first signs of clinical improvement. They could be elicited following a course of E.C.T. after the routine record had returned to normal.

(b) After the delta discharge induced by thiopentone, there followed in each experiment a quiescent stage in which rhythmic slow activity was absent from the record. After 6-7 treatments, sometimes earlier, a brief sensory stimulus now evoked a diffuse, though frontally predominant after-discharge of slow waves varying in duration from three to as long as ten seconds (Figs. 2a and b).

(c) The "quiescent" stage mentioned in (b) usually continued until the patient began to awaken 5-15 minutes later; during it slow rhythmic activity was absent even where it had been prominent in the routine E.E.G. (Fig. 3). The phenomenon could not therefore be attributed wholly to a decline in the effect of thiopentone, and there were other observations to suggest that it was due to overcompensatory enhancement in the activity of an inhibitory centre. On the assumption that barbiturates acted in the way suggested by the work of Moruzzi and Magoun (1949) and Lindsley, Bowden and Magoun (1949), this inhibition could be attributed to the activity of a centre situated in the reticular substance of the midbrain. Sensory stimulation at the height of the delta discharge likewise led to the inhibition of the slow activity for 2-5 seconds (Fig. 4), the effect thus being the converse of that resulting from stimulation during the inhibitory stage (*cf.* 1 (b)), when an identical stimulus would, after 6-7 E.C.T., evoke an afferent after-discharge. There was thus a suggestion of a reciprocal relationship between the excitatory and inhibitory centres of the delta discharge which seemed to behave as the mutually antagonistic components of some dual mechanism concerned with rhythmic activity in the brain.

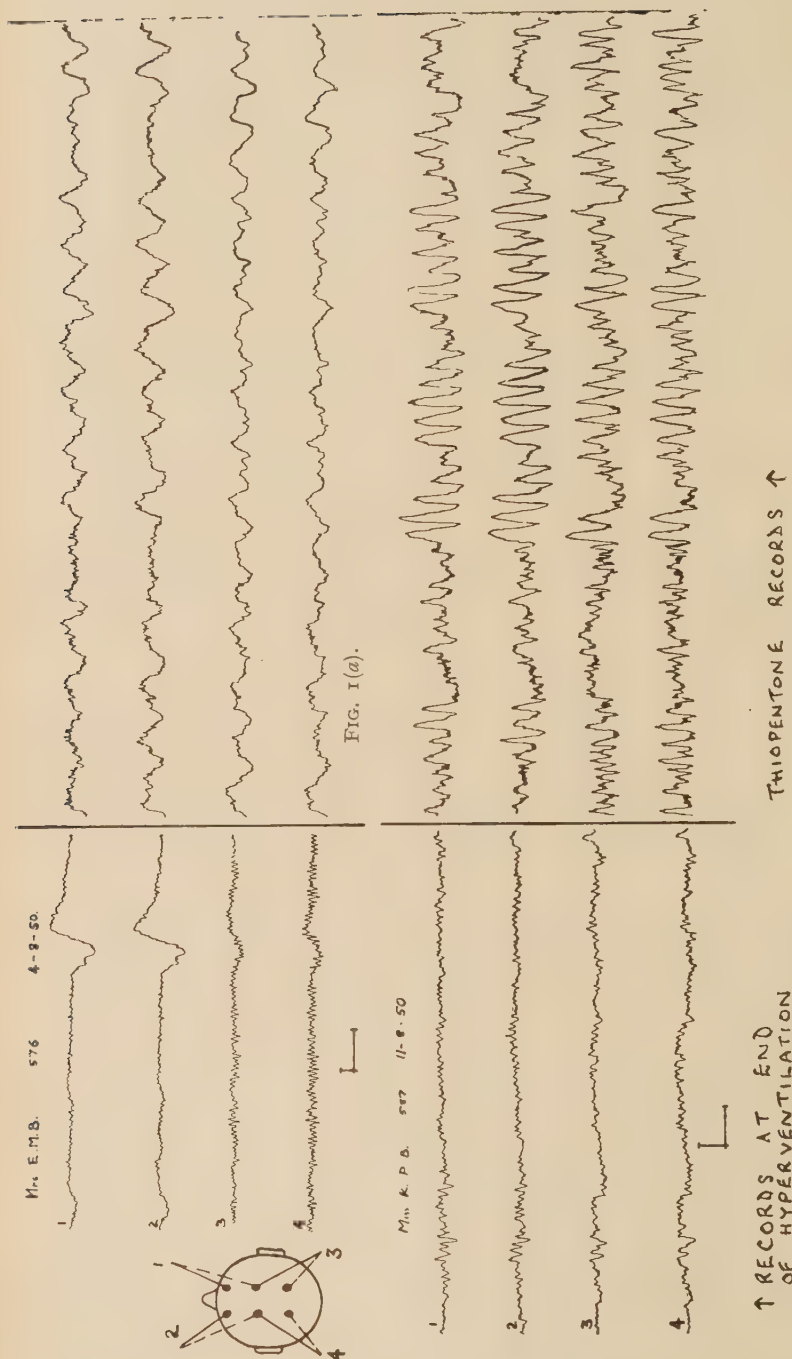


FIG. 1.—Records from two patients at different stages of treatment to illustrate the characteristics of the thiopentone E.E.G. during electro-convulsive treatment. Records on left show the E.E.G. at end of hyperventilation, on right after administration of thiopentone.

(a) Woman, aged 48. Two hours after third treatment the routine record shows no change; thiopentone evokes rhythmic slow waves in bursts, 100 μ v. in amplitude, synchronous in the two hemispheres. (Frequency unusually low at 1 c/s in this case. The solitary slow wave in the routine record is a blink artefact.)

(b) Woman, aged 39. Three days after sixth treatment hyperventilation evokes a few brief runs of low voltage 6 c/s waves. The thiopentone record shows high voltage paroxysmal sharp delta waves at 2 c/s. This record shows well certain

The evocation of such latent E.E.G. changes by thiopentone argues, in view of what is known of the site of action of barbiturates, in favour of a primary action by E.C.T. on the diencephalon. The characteristics of the change suggest an influence on some midline structure with access to all cortical areas,

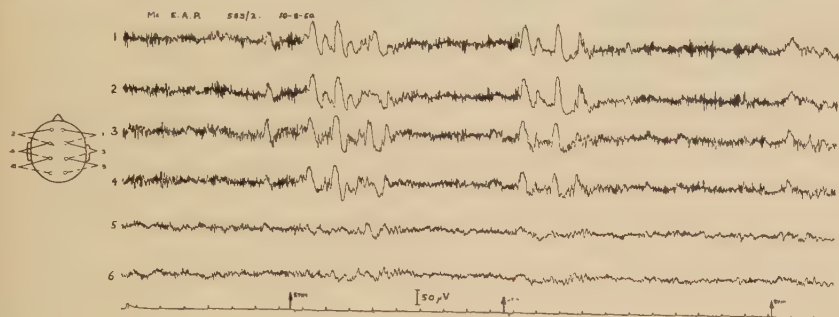


FIG. 2(a).

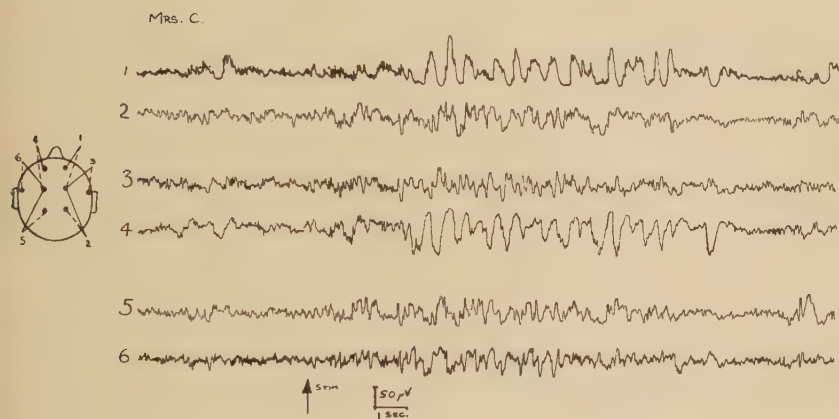


FIG. 2(b).

FIG. 2.—“Afferent after-discharge” evoked by sensory stimulation during thiopentone anaesthesia in patients having E.C.T.

(a) 36 hours after the 7th treatment each auditory stimulus evokes a high voltage frontally predominant delta discharge lasting 4 to $4\frac{1}{2}$ seconds. The record during and immediately after thiopentone injection showed paroxysmal bursts of identical form and localization, which continued for 120 seconds. Before E.C.T. stimulation in the same phase of the thiopentone record evoked only a brief, poorly defined response lasting half to one second, in which rhythmic, fast activity and a low voltage slow wave were combined.

(b) Prolonged after-discharge following a momentary pinprick on the dorsum of the hand in the inhibitory stage of the thiopentone record. Woman, aged 40, examined nine hours after the seventh treatment. There is an apparent interval of about $2\frac{1}{2}$ sec. between stimulus and the clearly definable onset of rhythmic after-discharge; this is occupied by rhythmic 10–14 c/s activity in random association with slow waves of low amplitude. The after-discharge shows marked frontal preponderance and continues for over 10 seconds.

though with some special relationship to the frontal lobes. This description suggests activation of the diffuse projection system of the thalamus (Morison and Dempsey, 1941a and b, 1942, 1943; Jasper and Fortuyn, 1946; Jasper, 1949), and the suggestion is underlined by the characteristics of the afferent after-discharge described above. For the diffuse projection system is the only known

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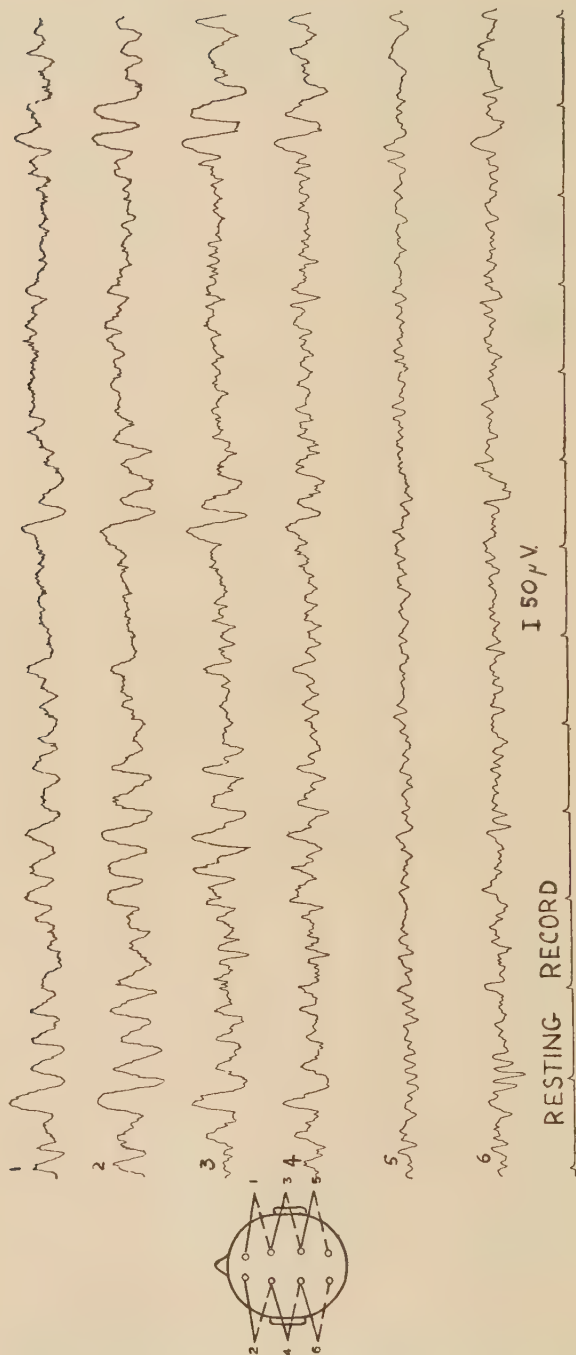


Fig. 3(a).

FIG. 3.—Effect of thiopentone when rhythmic slow activity is constant in the resting record.

(a) Woman, aged 36. Four and a half hours after eighth treatment resting record shows continual paroxysms of rhythmic, frontally predominant, bilaterally synchronous waves at 3 c/s. Over-breathing produced no significant change in the character of the record.

(b) After 4 c.c. thiopentone paroxysmal activity is rendered continuous. Waves are increased in amplitude (from 100–200 μ v. to 200–500 μ v.) but, in this case, decreased in frequency to 2 c/s.

(c) The continuous slow activity lasted 120 sec. and was followed by a quiescent or inhibitory stage (see text) in which rhythmic slow activity was absent from the record except where it was evoked in bursts by sensory stimulation. This stage lasted for 14½ minutes, when the patient began to show signs of awakening. The illustration shows inhibition of delta activity (seen in continual bursts in the resting record (a)), 13 minutes after termination of the slow wave discharge shown in (b).

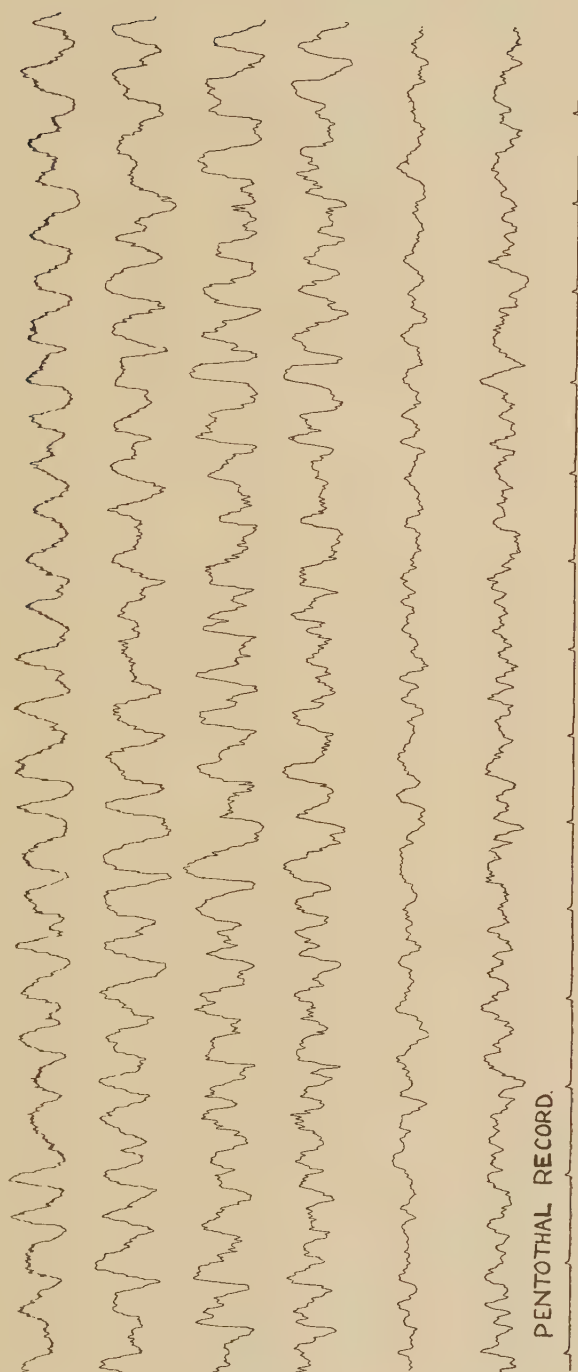
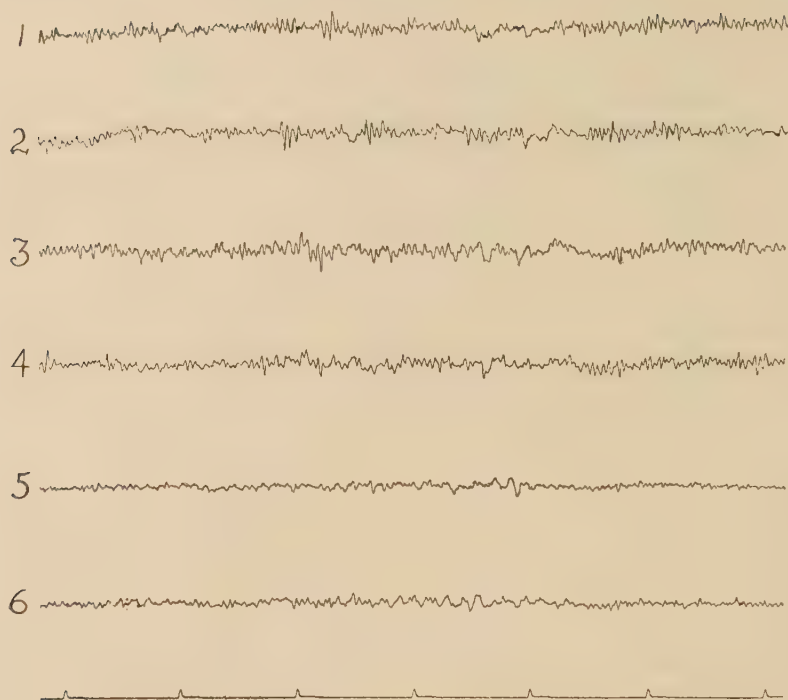


FIG. 3(b).



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FIG 3(c).

pathway to the cortex, whose excitation following a unilateral stimulus could give rise to a cortical response of such extensive and characteristic distribution. In further support of the suggestion is the fact that inhibition of the paroxysmal slow waves, similar to that described for responses from the diffuse projection system (Moruzzi and Magoun, 1949), has been observed in these experiments under conditions that suggest a similar physiological mechanism, namely increase in the activity of a mid-brain centre (*vide supra*). However, while it is difficult to see any alternative interpretation of these changes to that giving them a diencephalic origin, any more precise localization in the diffuse projection system of the thalamus can only be tentative in the absence of direct observations on the latter in man.

Clinical observation provides ample evidence, as Delay (1946) and others have pointed out, that E.C.T. does in effect exert an influence upon the diencephalon. Some of the most characteristic changes in the process of recovery are the rapid alterations in sleep rhythm, appetite, weight, water metabolism (Altschule, 1948) and the menstrual cycle. The amnesic syndrome produced by E.C.T. is strongly reminiscent of that following concussion, and it will be remembered that Jefferson (1943, 1951), among others, has marshalled a powerful body of evidence in favour of the view that the suspension of consciousness in this phenomenon is due to an influence on the diencephalon. Moreover,

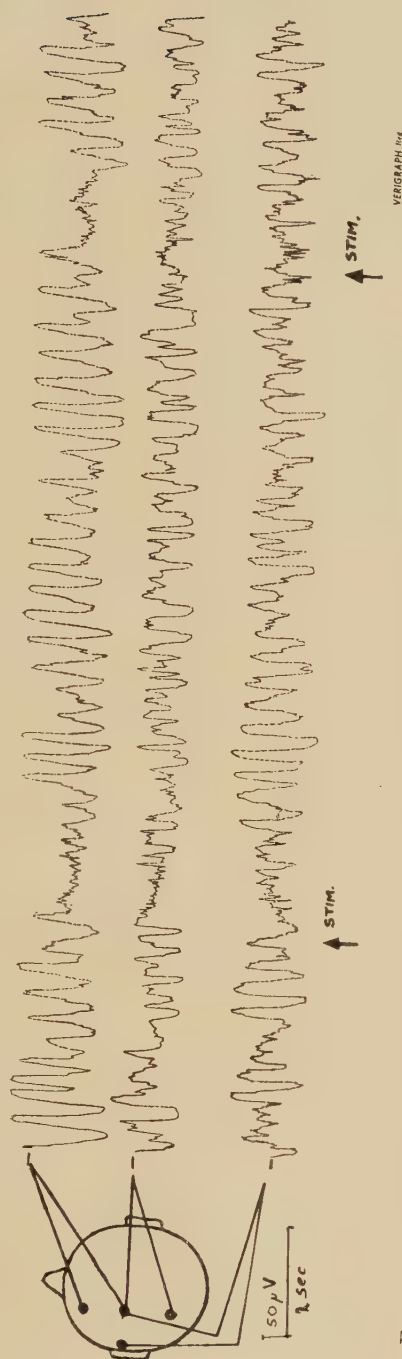


FIG. 4.—Inhibition of the thiopentone delta discharge by sensory stimulation. Woman, aged 50, who received 9 E.C.T. in 24 days. Thiopentone evokes very high voltage, rhythmic paroxysmal, frontally predominant delta waves. A momentary pinprick to the left and then the right hand causes inhibition of slow activity for about two seconds.

VERIGRAPH 104

following concussion as well as during E.C.T. a full-blown Korsakow syndrome may appear, and Gamper (1927) and Meyer (1944) have shown that a lesion in the diencephalon, probably in the corpora mammillaria, is at any rate one way of producing the condition.

The changes in the autonomic nervous system produced by E.C.T. have been described by Gellhorn (1943, 1949). He would wholly attribute the process of recovery to a prolonged "upward" discharge from the hypothalamic centre controlling the activity of the adrenal-sympathetic system. It is difficult to accept this view for a number of reasons. Although Gellhorn has demonstrated a hypo-activity of the adrenal-sympathetic system in schizophrenics, no such defect requiring correction has been demonstrated in depressive patients, in whom E.C.T. is a more effective treatment. It would, moreover, be difficult to reconcile this theory with the increased capacity for sleep shown by patients recovering with the aid of E.C.T., for it is Gellhorn's own view (Gellhorn, 1943) that there is parasympathetic predominance during sleep. Viewed as a whole, on the other hand, the changes reflect alterations in the activity of the diencephalic centres regulating sleep, appetite, menstruation, water metabolism, etc. Within the scope of such a generalized response by regulating centres increased activity of the sympathetic-adrenal system may well have some part to play. It is of interest in this connection that Earl Walker (1949) has hypothetically attributed a regulating function to the thalamic reticular system in which we tentatively localized the source of the E.E.G. changes, and has gone as far as to name it "the intracerebral division of the autonomic system." That in the paroxysmal high-voltage slow wave discharge we might be observing the activity of a part of the cerebrum with some regulating function is also suggested by the fact that it appears to have an inhibitory or damping mechanism, an essential feature of any homeostat that is to achieve stable conditions. The importance of vegetative changes for the process of recovery has formerly been emphasized by Ewald (1938), Ewald and Haddenbrock (1942), Cerletti (1940) and Delay (1946). Why they should be associated with the elimination of a psychosis becomes a little more clear when we examine the second line of evidence.

(2) *The Non-specific Action of E.C.T.*

If the effects of E.C.T. were to be accounted for in terms of homeostasis, it would have to be effective in a wide range of disturbances, for we would expect regulating centres to rectify different kinds of derangement of stable conditions. An examination of the available facts makes it clear that the action of E.C.T. is in fact non-specific. It influences depression as well as elevation of mood, stupor as well as hyperactivity, agitation or apathy, excessive spontaneity or retardation, poverty or flight of ideas. Not only affective disorders, but confusional states (Delay and Maillard, 1945, 1946; Roth and Rosie, 1951) and periodic exacerbations in the behaviour of deteriorated schizophrenics, barren of affect, are terminated. The temporary or partial remission which E.C.T. promotes in early cases of schizophrenia is often overlooked in discussions of its mode of action, but it has great theoretical significance. In epileptic fugues and twilight states its effect is usually dramatic.

According to some workers (Ewald and Haddenbrock, 1942 ; Bini, 1947) acute psychotic symptoms in general paralytics are temporarily alleviated.

An influence confined to affect cannot account for an action on such a diversity of clinical phenomena. It would seem more likely that E.C.T. tends to eliminate qualitatively new behaviour patterns that are recently acquired, and to facilitate restoration of the more firmly established framework of pre-psychotic personality. The fact that in different psychiatric disorders E.C.T. is effective in varying degrees does not in any way invalidate this view, which postulates that in all of them the effect is of the same non-specific kind; total behaviour is directed with more or less success towards the relatively well-established pattern that prevailed in the individual's premorbid state.

In this light the somatic and electro-encephalographic changes produced by E.C.T. acquire a biologically purposeful character,* for they appear as a concerted response by the homeostatic centres in the brain directed towards the restoration of the most stable and integrated organization of cerebral and metabolic activities hitherto attained. This is not an unexpected response to a succession of apparent threats to the organism's integrity, represented by the passage of electric current through its master organ, the brain. It permits of an explanation of the positive and negative effects of E.C.T.—the former the stimulation of vegetative functions, the latter the elimination of psychotic behaviour—in terms of a single process, the homeostatic restoration of equilibrium.

There is thus a differential effect as between recently acquired behaviour patterns which tend to be eliminated and the attributes forming a long-established and coherent system (i.e., the patient's basic personality) which are restored intact. A similar phenomenon is seen in the limited field of cognitive function where memory for recent events is affected with preferential severity while basic intelligence is unaltered (Zubin and Barrera, 1941 ; Roth and Hetherington, 1950).

Certain consequences would follow from the theory as stated so far. We would expect to find, for example, that the sharper the distinction between the morbid and premorbid behaviour patterns, the greater the likelihood of a successful outcome from treatment. This is in fact the case. E.C.T. has found little application in the treatment of neuroses, disorders which may be regarded as exaggerated versions of the patient's normal behaviour and, hence, firmly rooted in his constitution. Where there is some newly acquired pattern of behaviour in a neurotic, as in the case of a depressive episode in a severe obsessional, E.C.T. will usually cure the depression without, however, making any significant impression upon the neurosis. Similarly, in the case of schizophrenia E.C.T. makes least impression when the disorder commences insidiously, and in patients whose premorbid personality has had some obvious affinities with the behaviour patterns imposed by the psychosis. Thus it is well known that in hebephrenic and simple schizophrenia little or no change can be anticipated, while catatonic and paranoid forms show at any rate a tendency to

* Since any suggestion of teleology arouses discomfort in some scientists, I should like to cite the passage from E. von Brücke recently quoted by Professor Franklin in his Oliver-Sharpey lectures. "Teleology is a lady without whom no biologist can live. Yet he is ashamed to show himself with her in public."

transient remission. This is not to be accounted for in terms of the period that usually elapses before the patient is likely to present for treatment. In the case of the first two conditions prognosis is poor, irrespective of duration before they come under medical observation.

It has become generally accepted that in psychosis in general a good pre-psychotic personality, acute onset and floridity of clinical picture are relatively favourable indications in prognosis, whereas, other things being equal, early or insidious onset of a psychosis or its prolonged duration before treatment make for an unfavourable outcome. All such pointers may be related to the single factor of degree of differentiation between psychotic and premorbid behaviour. This is not to say that qualitative distinctions are of no consequence. Psychoses differ in their malignancy; it is not difficult to see, for example, why, other things such as age equal, a fundamental disorder of thought, volition and affect, such as schizophrenia, should show little tendency to sustained remission as compared with a depressive illness in which the mental disturbance may be largely attributable to the morbid affect.

Some authors (Freed, Spiegel and Wycis, 1949; Sargant, 1951) consider that patients with prominent tension and anxiety respond poorly to E.C.T. The favourable outcome of cases of depression occurring during the involutional period or in old age conflicts with this view, for tension is frequently marked in these cases. The question that arises is whether it is tension as such, or some associated factor that causes the poor results observed by these authors. Tension is a common symptom in the so-called "neurotic" depressions of young patients, and it is reasonable to inquire whether it is not a general neurotic instability rather than tension that is linked with the poor result. Even in these cases where depressive features are clear-cut a brief remission is often produced by E.C.T., not, in the author's experience, often in a setting of clouding of consciousness or gross amnesia. Such a temporary influence on a mental disorder, seen also in schizophrenia, is not to be overlooked. Even where most effective, as in involutional melancholia, E.C.T. does not prevent the tendency to recurrence when this is present. In other words the effect of E.C.T. is never other than temporary, and its short-lived therapeutic effect in these disorders cannot be regarded as physiologically distinct, but different only in degree from that in conditions in which a much more enduring effect usually makes it the treatment of choice.

It will be seen that the two lines of evidence described so far are mutually supportive, for we would expect the activity of regulating centres to exert a non-specific effect and, conversely, an influence on different kinds of mental disorder is consistent with an action of a homeostatic kind.

(3) *The Dedifferentiation of the Electrical Activity of the Brain Produced by E.C.T.*

How does E.C.T. produce such a differential effect in the brain on recent, as distinct from long-established, behaviour patterns? A study of the E.E.G. changes provides a possible answer, although, in our present state of ignorance as to the origin and function of rhythmic activity in the brain, this necessarily involves a certain amount of speculation.

After a long course of treatment the rhythmic activity of diencephalic origin causes large areas of cortex to beat in unison with a waxing and waning rhythm at 2-3 c/s. When there is little apparent change in the cortex in full consciousness at an early stage of treatment, this beat is readily transmitted to it in light sleep under thiopentone. The typical response described above is not identical with spike and wave activity, but is none the less evocative of Lennox's famous description of the latter. "The large waves represent not a suppression or an augmentation, but a synchronization of various discharging cell clusters. There is integration of activity as regards timing, but disintegration as regards the delicate and complicated interplay of various discharging nuclei. The harmony of the symphony orchestra has become a single note." There is, in other words, a dedifferentiation of the electrical activity of the brain.

What little we know of such slow rhythms in nerve cell clusters suggests that they are associated with states of quiescence in nervous function. If we assume that these rhythms reflect activity in neurones, and the available evidence favours this view, the reason is not far to seek in the case of the cerebral cortex. The highest forms of mental activity, as in conscious thought, are specific, and can involve only a limited number of cortical neurones; attention can be effectively directed only to one line of thought at a time. Less discriminate and more diffuse forms of mental activity are associated with lower levels of consciousness as in sleep and states of mental confusion, when many streams of thought seem to proceed simultaneously. Such thought processes hence lack the definition and purposefulness that characterize the highest forms of mental activity. It is perhaps for this reason that they are associated with an electro-encephalogram which is slower, higher in voltage more rhythmic and, therefore, more undifferentiated than those to be seen during mental activity in full consciousness.* This interpretation receives some support from the fact that a discharge of great amplitude occurring simultaneously from all cortical areas seems to be incompatible with the specific or differential neuronal activities underlying conscious behaviour, for where it evolves rapidly, as in the highly synchronized discharge of the epileptic seizure, it is associated with sudden loss of consciousness.

Now experience with psychoses of long duration has taught us that their resistance to alteration is, among other things, a function of time (Kalinowsky and Hoch, 1947). Thus many schizophrenics who are submitted to prefrontal leucotomy within two to three years of the onset of the psychosis make a good social recovery, but very few cases improve after, say, 20 years of illness. This suggests that in its early stages a psychotic behaviour pattern might be based upon some form of continuous neuronal activity, which ultimately results in subtle structural alterations that are irreversible. It is possible that the highly synchronized beat we saw imposed upon the brain might be inimical to such continuous activities in neurones, though powerless to alter behaviour patterns that have acquired a structural basis no longer dependent upon them. The

* That the relationship between the electroencephalogram and level of awareness outlined here holds as a general rule is all that need be assumed for the purposes of the argument pursued. This general rule requires some qualification, but it is hoped to discuss this subject in a separate communication.

premorbid personality, whose relative stability suggests more or less permanent neuronal configurations, would accordingly be left intact, while a psychosis, unless its duration or malignancy had resulted in such permanent changes, would be eliminated. Emphasis must be laid in any such explanation upon the remarkable resistance to alteration of the integrated organization of affective, conative and cognitive attributes, or basic personality, to alteration once it has reached maturity in adult life. We know from clinical experience that it may emerge fundamentally intact after long periods of coma, extensive cerebral ablations, certain types of cerebral infection and, in some cases, after treatment of a protracted mental illness. A gross dedifferentiation of the electrical activity of the brain, such as that produced by E.C.T., might, therefore, cause the elimination of all such patterns of behaviour that have not yet become part of this integrated organization while leaving the latter basically unaltered.

(4) *The Biological Significance of Epilepsy.*

Since such investigation into the mode of action of E.C.T. shows the epileptic fit in the setting of a generalized, purposive response by regulating centres, it is pertinent to inquire whether the fit itself might not form an integral part of this response. Is there, in other words, anything to suggest an association between epilepsy and regulation? Only tentative and hypothetical answers can be given to this question at the present time, but an examination of the available evidence suggests some interesting possibilities. The epileptic fit may, of course, be provoked in any human being as well as in members of a number of animal species by adequate stimulation. This in itself should lead us to search for some physiological function that it may subserve, for it would be strange if a phenomenon so universal and easily evoked among the species highest in the evolutionary scale should be wholly pathological in its significance. Cerletti (1942),* who was the first to seek for some biological meaning to the epileptic fit, concluded that it was "une réaction de terreur-défense." He claims, moreover, to have isolated from the brain of convulsed rabbits a substance, "acroagone," which has defensive properties conferring immunity in animals against a number of infections and also exerting a therapeutic action in certain human mental disorders. His results are not as yet confirmed outside Italy; it may, moreover, be questioned whether the tonic and clonic phases of the major epileptic fit are in fact expressions of terror and defence respectively. Nevertheless there are certain facts to suggest that Cerletti's theory may have been an important step in the right direction, and that the efficacy of the major epileptic fit in certain mental disorders may be only one example of its positive physiological role.

(i) The epileptic fit may be provoked by a bewildering variety of changes in the internal environment of the organism. Thus drastic alterations in the CO_2 or oxygen concentration of the blood, a steep fall in blood sugar and excessive

* This requires correction. He was preceded by Muskens ("Epilepsy." London, 1928) who held that the fit had a detoxicating action. Muskens also quoted the work of earlier writers such as Turtschaninow and Hill, which suggested that the fit was part of a defensive or protective mechanism.

hydration are all productive of convulsions or changes of an epileptic kind in the electroencephalogram. Attempts to find a factor possessed in common by all these changes have not succeeded. This is not surprising in view of the fact that not only are these metabolic stresses diverse, but changes of opposite sign are known in some cases to produce the same result. Thus alkalosis produced by hyper-ventilation tends to provoke a fit or E.E.G. changes, but convulsions may likewise be precipitated by inhalation of a high concentration of CO_2 (Pollock *et al.*, 1949; Meduna, 1951). Another example is the occurrence of fits in hypertensive encephalopathy, but also during the faints often observed in blood donors (Sharpey-Schafer, 1951). The fit may, of course, result from a general breakdown of homeostasis. There are observations suggesting that another possibility deserves investigation. In one of the serious threats to an organism's integrity, namely, the coma induced by narcotic poisoning, the most effective therapeutic agents are convulsants. In the case of barbiturate intoxication, for example, picrotoxin is the most powerful resuscitant. There is also the therapeutic action of E.C.T. in a variety of mental states to raise the possibility that the fit might have some part to play in the mechanisms mobilized during metabolic stresses for the restoration of equilibrium.

In such terms of homeostasis the special propensity for convulsions shown by children acquires a possible significance, for the instability of their metabolism is perhaps liable to expose the brain to extreme conditions that might endanger its integrity.

(ii) In certain epileptics periods of severe mental disturbance culminate in and appear to be terminated by an epileptic fit. This fact is well known to those who have epileptics under their care for long periods. That the fit in such circumstances is likely to be more than an undesirable complication of the emotional disturbance is suggested by the fact that such conditions as, for example, the fugues and twilight states already mentioned may usually be terminated by an artificially administered fit.

(iii) There is a large body of neurosurgical and experimental evidence (Penfield, 1941; Jefferson, 1943, 1950) to suggest that the control of consciousness is maintained from the diencephalon and not the cerebral cortex. Thus cortical stimulation and even extensive cortical destruction do not cause a loss of consciousness, whereas stimulation or injury in the neighbourhood of the third ventricle invariably produces a lapse into coma. Vigilance or wakefulness, of which consciousness, as we know it in man, may be regarded as an extrapolation, is a primitive function shared by a large part of the animal kingdom (Delay, 1946). Its control is thus not unexpectedly localized in a part of the brain that contains the regulating centres of his vegetative life.†

* Hill (1948) has also observed epileptic dysrhythmia during the stage of recovery in some periodic catatonics. He considered that the changes were related to the improvement in the clinical picture. The finding is of considerable importance, but the fits in all his cases occurred after the catatonic phase. Unexpected also was the finding of such changes in schizophrenics, in whom homeostasis is said to be defective, while no changes are on record in "functional" mental disorders with no demonstrable deficiencies in regulation.

† This is not to say, however, that the diencephalon is the "highest level" in the brain or the site of conscious thought, any more than a searchlight beam can be said to contain the object on which it is focused.

This evidence is at first sight difficult to reconcile with the fact that localized cortical scars, infarctions and areas of agenesis are regularly associated with major epileptic fits. Is it possible that the latter are compensatory reactions by sub-cortical centres to the pathological patterns of activity originating from the cortical regions? The work of Van Harreveld (1947) has in fact shown that decortication causes no significant alteration in the characteristic features of the epileptic fit.

In the so-called "idiopathic" epileptic there is no cortical lesion to account for the epileptic fit in the way suggested, but, as Davies (1950) has pointed out, regulating devices themselves have their disorders, one type of failure of normal homeostasis being over-sensitivity or under-damping of the regulating mechanism. Where there is no discoverable cause provoking it, the epileptic fit might, therefore, reflect, as Davies suggests, a primary disorder of one of the mechanisms regulating cerebral excitability.

The reasoning pursued in this section is admittedly speculative, but permits of an explanation for a variety of phenomena of obscure causation in terms of a single fundamental process; its validity may, moreover, be tested by a number of experiments.

If the epileptic fit is part of the apparatus for the maintenance of a relatively stable pattern of activities in the brain, why, it may be asked, has natural selection not rendered this apparatus more sensitive and efficient? Why, in other words, are not psychoses self-terminating by means of spontaneous fits? The answer that suggests itself is that an apparatus so efficient might also have been sensitive enough to send us into a fit each time we were moved to tears or burst into laughter, and there would be no selective advantage attached to such refinement. In this light, however, the association between outbursts of rage or laughter and major attacks in epileptics possibly acquires a new significance.

SUMMARY.

(1) The main results of an investigation into the changes in the electrical activity of the brain produced by E.C.T. are summarized. Evidence was obtained that the primary effects of E.C.T. are on the diencephalon; serial E.E.G. studies suggested a cumulative influence on some midline structure with access to all cortical areas, though with some special relationship to the frontal lobes.

(2) These E.E.G. changes and the rapid alterations of sleep rhythm, appetite and other vegetative functions suggest that a concerted response is evoked from diencephalic regulating centres.

(3) The evidence that E.C.T. acts on new and recently acquired behaviour patterns in general is outlined. In the light of this evidence the total changes produced by E.C.T. acquire a biologically purposeful character, for they appear as a concerted response by homeostatic centres in the brain directed towards the restoration of the most stable pattern of cerebral and metabolic functions hitherto attained.

(4) It is suggested that the dedifferentiation of cerebral electrical activity produced by E.C.T. might act with preferential severity on a new, recently estab-

lished behaviour pattern such as a psychosis, leaving the long-established basic personality intact.

(5) The possible significance of the findings for the general problem of epilepsy is discussed. Evidence in favour of the view that epilepsy might have some positive physiological function, in relation to the maintenance of a relatively stable pattern of activities in the brain, is outlined.

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IMMEDIATE EFFECTS OF LEUCOTOMY ON CEREBRAL FUNCTIONS AND THEIR SIGNIFICANCE.

A PRELIMINARY REPORT.*

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THE subject of this investigation is the study of the immediate mental changes after standard leucotomy up to a time when the more acute manifestations of the brain operation have subsided and a stage of stabilization has been reached. Altogether twenty cases were examined, most of them schizophrenics. The observation time was between eight weeks and twelve months. The patients were examined in the first eight to ten days every day, and later at longer intervals according to their stabilization. In about half of the cases a detailed assessment of the patient's personality and intellectual faculties with a battery of tests was made before the operation. An assessment was also made of the patients' special abilities and knowledge, their general outlook and interests that had not been covered by the routine testing. The aim of the investigations was first to obtain a detailed picture of the acute condition following the operation, generally referred to as a confusional state, and to follow up the reorganization of these defects. Our next objective was to find out what significance these initial changes, or particular components of them, might have on the final result of the operation.

We were able to distinguish two groups of symptoms, one containing variable symptoms present in some cases, absent in others. The symptoms of the other group were invariably present in all our patients who showed a post-operative change of personality. We extracted such symptoms which appeared to us of an elementary character; they are, for the first group, perseveration, inertia, verbosity, manic-like condition, associative poverty, disorder in thinking and conceptual weakness. For the second group, amnesic syndrome, disorder in time, discontinuity of pre-operative ideation, lack of curiosity and urgency.

We found that from the acute post-operative picture a more permanent mental change of a well-defined character may arise without the presence of any of the variable symptoms. In our attempt to explain this change we may therefore disregard the variable features and confine our discussion to the constant post-operative symptoms.

CONSTANT (OBLIGATORY) SYMPTOMS.

I. *Retention Defect.*

There is from the beginning, mostly from the first or second day after the operation onwards, a very good immediate retention. The patients retain a

* Paper delivered at the Annual Meeting of the Royal Medico-Psychological Association, Dumfries, July, 1951.

particular question or test as long as they are not distracted by another question, but any previous question is usually extinguished by a following one and cannot be recalled.

However, the span of memory is very short. Patients when asked after examination to give an account of the interview can produce only a small proportion of items, and frequently are unable to recollect anything at all. The recollection of day-to-day happenings in the first few days after the operation is almost *nil*.

The poor retention lasts at least a week, but some retention impairment in cases with severe post-operative pictures may last several months.

2. *Amnesia.*

(a) *Anterograde Amnesia.*

About half of our patients could not remember the post-operative bandage round their head, which was changed for a plaster round their forehead at the end of the fourth day. For the first four to seven days a number of the patients could not recall the examiner's daily visits at their bedside. Others thought they remembered seeing him once or twice during this period. A great proportion of cases remembers very little of the ward in which they stayed for a week to a fortnight after the operation. They may not know what bed they were in; they cannot say for how long they were kept in bed or whether they had been kept in bed at all. They are not sure when they were allowed to get up or when they first dressed. They are usually well aware of the vagueness of their recollection of this period. The long daily sessions with the examiner in which they proved to be attentive and co-operative were also included in the amnesia.

(b) *Retrograde Amnesia.*

Although we found retrograde amnesia in all our cases, it is usually much less complete than the anterograde amnesia. A number of patients cannot recall being prepared for the operation. Patients who had several interviews for testing purposes during the fortnight to three weeks prior to the operation may not remember anything at all, or may have only a vague recollection. They may not recollect any of the test material used again after the operation. This occurred in patients who before the operation were able to give all details of an interview after more than a week had passed. Many patients cannot recall the interview one or two days before the operation in which the operation was discussed. This is specially noteworthy, as the mnemonic value of such an interview must be considered as particularly high. In two cases there was a long retrograde amnesia extending from two to three months. Generally the retrograde gaps are rather patchy and do not break up the temporal continuum; so patients may, for instance, remember a special memory test given just before the operation, but they may have forgotten many other details which took place prior to it.

3. *Temporal Disorder.*

This is one of the most outstanding phenomena following the operation. There is, on examination, no definite defect in the estimation of time just passed, but when one goes further back their orientation for time is found to be very much disordered. Not only has a particular experience lost its definite place in time, but also the relative temporal order of various happenings has become involved. This applies not only to the material for the post-operative period, but also for experience before the operation. The patients may remember things which happened one or two days before, but they are never sure on what day they actually occurred. They are not sure when the last interview had taken place, cannot say what date it is or what day of the week; they may date to a period before the operation particular happenings which took place after the operation or a few days ago.

The temporal disorder is always associated with some loss of memory for data, but in some cases this loss is only slight and the temporal disorder is then the outstanding phenomenon. The duration of the severe disturbance in time relation was at least a fortnight, and always outlasted the retention defect for data.

4. *Discontinuity of the Pre-operative Ideation.*

The discontinuity of the past does not merely consist of loss of material for a circumscribed period of time. It is common to find, for a period of a week to a fortnight after the operation, that the patients are unaware of their pre-operative ideas and are unable to give any information about them, however systematic and forceful they had been before. In a few cases in which the amnesia was very protracted the material was extinguished altogether and could not be evoked during the time of observation, which lasted from six to eight months; but with the gradual lifting of the amnesic syndrome most patients can recall what occupied their mind before, and they often give the information with greater readiness and detail than before the operation. They do not necessarily correct these ideas, but with great regularity the patients agree that the thought material has become more quiescent, that it does not emerge spontaneously with the same frequency and intensity as before, nor does it intervene whatever the situation may be. Most instructive are those cases in which the amnesic syndrome was only slight, and in which all other defects were absent from the beginning. Some of these patients stated, when referring to their previously predominant ideas, that these had become rather distant and vague; others described them as impersonal and not so immediate. They were all in agreement that these ideas came up only fleetingly with less intensity and frequency.

As to the actual thought content of the patients, even after the acute post-operative phase has subsided, this remains poorer than one would expect from their pre-operative personality and interests. When questioned many of these patients will say that there is nothing particular in their mind and that nothing comes up on its own. Their thoughts are usually only connected with daily routine and, as one of the patients put it, the content of thought is almost entirely elicited by external situations. There is, however,

when these patients are tested, no indication that the associative power is diminished at this period.

This discontinuity of the past was usually evident in our cases from the first day after the operation until the end of our observation, with a few exceptions of cases who had an early relapse. A few cases showed an interesting deviation. After the pre-operative attitude had continued a sudden change took place, in one case one day, in another, two days after the operation. In a few other patients the change came on gradually. They expressed for a few days after the operation their pre-operative ideas with the same vigour as before, but became then gradually less outspoken until they stopped producing them spontaneously.

5. *Lack of Curiosity and Urgency.*

The patients take things as they are without adopting an inquiring attitude, whether it concerns themselves or their surroundings. They do not see a situation in a problematic setting, and there is no tendency to explore such a situation. They will rarely initiate a conversation, but will join in when directly approached. In an interview they do not ask questions. They seem to have no requests. This lack of curiosity and urgency may be the cause of inertia; but it is not necessarily connected with it, as it can also be found in those patients who seem to be elated.

DISCUSSION.

In analysing the constant symptoms I will first discuss the amnesic syndrome. Compared with the acute amnesic syndrome of other origin, the syndrome in our cases is superficially very similar to the post-concussional amnesia, but closer examination shows some significant differences. Our patients are usually, almost from the start, quite alert and attentive when stimulated, and there is no sign of fatigue, even in prolonged testing. There is also a remarkable ability to direct attention to a particular object and fix their attention on this object. In contrast to the acute amnesic syndrome of any other origin, a lowering of intellectual functions is not necessarily associated with the amnesic syndrome in our observation. There are also particular features in the amnesia itself. The anterograde amnesia in no way goes parallel with the lowering of the general intellectual functions; there may be an amnesia for a period in which the patients were clear, alert, and with intellectual functions intact. There is also a difference in the retrograde amnesia. In our cases, in contrast to the acute amnesic syndrome of other origin, most of the material which could not be recalled during the period of restitution remained lost. Finally, there is a marked preponderance of the temporal disorder; in some patients it was almost the only sign of the disorder, and usually out-last-ed the memory defect for data. The amnesic syndrome of our cases has therefore some specific features which might suggest that the focal lesion in the brain is more significant for its causation than a possible general brain damage.

However, the amnesic syndrome here described can hardly account for the

post-operative change in attitude and behaviour. For this the discontinuity of the pre-operative ideation seems to be of greater significance, and I want to present the following interpretation :

We may assume that there is, both in normal persons as well as in well-integrated psychiatric patients, a basic attitude, which arises from past experience, and is partly organized and partly fluid. *Its organization and synthesis to a definite pattern peculiar to an individual may be called the ideatory scheme.* When mental activity involving approach and conduct takes place this scheme has to be activated, so as to form the ground on which the mental process may progress, securing thereby the continuity of the personality. This process has been profoundly altered in our patients. In a few cases the pre-operative ideatory scheme seemed to be almost altogether extinguished. In the great majority of patients it is still present, but the mechanism responsible for its presentation has been put out of order. As an operative scheme it appears, as we have seen, only rarely in the foreground, and when it does so its appearance is transitory and distant and the exposure time is too short to render it effective. It fails to take part in field formation, to provide the ground from which the figure, that is the particular mental response, may emerge. The ideatory scheme blocked and the flow of fluid background material reduced, there is no material from which to build up or to elaborate the situation to a problem stage. Therefore, no tension can arise and the patient feels unconcerned and at ease. Objectively the condition is more complex. There is a significant contrast between the patient's intellectual performance in test conditions and the patient's conduct. The defect of acquired knowledge, as we have seen, is, if present at all, only transitory. To use it skilfully no individual ideatory scheme is required, nor is the background material we referred to necessary. However, when the ideatory scheme is inactive and background material is not forthcoming, disorder of conduct will necessarily occur. Approach and conduct will lack the personal note and it will become hazardous ; short-circuit reactions will appear if the patients have to respond to situations. They will then seem uncontrolled, childish and selfish. There will be little motivation to approach actively a situation, no driving force to create the curiosity to explore into situations, nor any urgency to solve problems. The patients will, therefore, appear passive, disinterested and detached.

The discontinuity of ideation as distinct from the amnesic syndrome presents merely a second stage in the post-operative course. It might well be that the defect in presentation of past experience is the more persistent part of the amnesic complex, exposed after the more massive signs have subsided. One could see the connecting factor between these two phases in the temporal disturbance. The temporal disorder, one of the outstanding symptoms in the amnesic syndrome, seems also to persist, though less well defined, in the next phase. There is a certain timelessness in the attitude of the patients ; they do not experience any boredom as to the time just passed, nor is there any urgency felt as to the time to come. Time seems to have become an unorganized continuum. The remoteness with which some of the patients experience the past might be a further indication that the time factor is involved.

A lesion which is able to block ideation and to prevent the presentation of the ideatory scheme will necessarily have a beneficial effect upon a variety of psychiatric conditions in which, as a common factor, the ideation interferes with a balanced conduct. One would also expect that the more systematic and integrated the scheme has been the more striking will be the operative result. This is so far confirmed by our observations. Although this may be applicable so far as groups are concerned, it is, however, difficult to predict from case to case. There were in our series cases in which the fundamental change we described was so complete as to eliminate the interfering ideation altogether. In others this change was less complete and the result was correspondingly not wholly satisfactory. There were, finally, cases in which the pre-operative mechanism after its initial elimination re-established itself and the patient relapsed. There might be various factors responsible for such difference in reaction. Clinically, the following observation seemed to be relevant to this problem: We found no definite correlation between the initial complexity of the post-operative picture and the subsequent altered conduct. Cases in which the initial defect consisted only of a slight amnesic syndrome showed subsequently the characteristic change, and the mental symptoms practically disappeared; on the other hand, in some cases with a more complex initial post-operative picture the effect was less satisfactory. The additional manic reaction was no exception; one of the patients with a most prolonged and most marked manic reaction had an early relapse. It seems, therefore, that if the complexity of the post-operative symptoms is an indication of the extent of the operative damage, the crucial area is relatively small. There is, however, the possibility that the relative permanency of the result may depend upon the extent of the damage, i.e., to what extent the relevant connecting thalamo-frontal fibres are severed. We have the impression that the more severe and protracted the amnesic syndrome is, the more permanent is the result. Similar relations may exist regarding the variations in degree of blocking of the ideatory scheme. We found in some cases an estrangement and neglect, in others an unawareness, and in a few cases complete loss of the pre-operative ideation. An anatomical investigation in cases in which the post-operative course is carefully studied may give the final answer to this question.

Considering finally the various degrees of consciousness of the previous ideation, there seems to be some parallelism with the pathology of the body scheme. One could imagine that the severance of the anterior connections of the thalamus with the cortex has a similar effect upon the ideatory scheme as that of its posterior connections has on the body scheme.

PROBLEMS IN THE DIAGNOSIS AND CLASSIFICATION OF MENTAL DISORDER IN OLD AGE ; WITH A STUDY OF CASE MATERIAL.*

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I. INTRODUCTION.

Recent statistics of old age mental disorder have drawn an alarming picture of rising rates of admission to mental hospitals in many parts of the world. One of the predictions made on the basis of such statistics has been that old age psychoses might, in due course, relegate schizophrenia to second place in number of admissions. There are, however, dangers in drawing conclusions about a complicated problem, such as mental disorder in old age, on statistical grounds alone. Before the figures can be properly evaluated more detailed information about the social, economic and, above all, clinical aspects of the problem will be required than is available at present.

In the sociological field there are already observations on record suggesting that the trends described are not inevitable. The work of Faris and Dunham (1939) has shown that the incidence of old age mental disorder, in so far as it is reflected in number of admissions to hospital, is dependent upon the protection of the old against social insecurity. A number of the available facts favour the view that the discrepancy between the vast increase in the rates of admission of old age mental disorder to mental hospitals in the United States and the relatively smaller changes in Britain might well be due to differences in the social and economic status of the old in the two countries (Roth, 1950).

In the clinical field a need for detailed information about the natural history of different types of mental disease in old age has been created by a number of recent developments. At the beginning of this century the mental diseases peculiar to old age were subdivided into the senile, arteriosclerotic and pre-senile psychoses, as a result of the work of Alzheimer, Binswanger, Kraepelin, Pick, Simchowicz and others. The pre-senile psychoses were recognized from the outset as a numerically insignificant group in comparison with the other two. The principal lines of demarcation thus drawn between cerebro-vascular disease and senile cerebral degeneration on the one hand, and between both

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these and neuro-syphilis on the other represented a great advance. With the increasingly clear differentiation of neuro-syphilis, it led to the important distinction between disorders pursuing a fluctuating course with emotional lability, cerebro-vascular symptoms and late retention of insight on the one hand, and on the other the condition of senile psychosis, an illness of insidious onset pursuing a uniformly progressive course with steadily augmenting mental decay. However, reasons have appeared in recent years for doubting the specificity of the pathological changes associated with these two disorders. Senile plaques and neuro-fibrillary changes have been shown to occur in healthy old age (Gellerstedt, 1933), as well as in the brains of chronic psychotics who merely live to be old (Newton, 1948). The relationship of arteriosclerotic change to old age in general has been called into question (Hirsch, 1945; Riese, 1946). The work of Rothschild (1937, 1942, 1945) has shown, moreover, that even in established old-age psychoses there is little relationship between the quantitative severity of changes in the brain and the clinical picture. This doubt thrown upon the relevance of the cerebral changes, even if only in a quantitative sense, shows the need for more detailed clinical observations, if we are to achieve a soundly constructed and practically useful classification of mental disorder in old age.

2. THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA IN OLD AGE.

There has been a tendency in the psychiatric literature of the past fifty years to over-emphasize the importance of senile, pre-senile and arteriosclerotic psychosis to the relative neglect of other disorders in old age. Yet even dementia may have a number of other causes. Thus cerebral tumour commonly presents with intellectual deterioration and personality change. Papilloedema is often absent and the diagnosis is easily missed, as was the case in 40 of 100 successive cases seen at post-mortem at the Mayo Clinic (Moersch *et al.*, 1941). In a recent paper Sachs (1950) has emphasized the frequency with which meningiomas, which invade the brain only secondarily, may present with a rapidly progressive dementia as their earliest manifestation. Six of the eight cases he reported were over 55, three more than 65 years of age. The classical florid symptoms of G.P.I. tend to be in abeyance, intellectual decay and affective poverty often dominating the clinical picture. The signs of disseminated sclerosis presenting late in life often herald a rapidly progressive dementia; it has been shown recently (Einarson, Neel and Strömgren, 1946) that such cases are commonly examples of a late form of Schilder's disease. Intellectual atrophy is likewise often prominent in the cerebellar degenerations of later life, and may be the consequence of head injury, chronic heart failure, uraemia or other protracted physical illness. On the other hand, positive neurological signs are not necessarily relevant to a co-existing psychiatric disorder, for Howell (1945) has shown that inactive pupils, absent deep reflexes and patchy analgesia of limbs are common in the old, even in the absence of a definable neurological lesion. Some help may be obtained in establishing the diagnosis from special methods of investigation such as the air encephalogram (Delay 1944*a* and *b*; Ostergaard, 1945; Mallinson, 1947*a* and *b*) and the E.E.G. (Hill,

1946). However, in the case of the former, serious mistakes may be made through a failure to take into consideration the normal variation with age in the appearance of the ventricles and subarachnoid space (Heinrich, 1939). Likewise in the case of the E.E.G. an apparently severe abnormality may be due to a temporary and reversible clouding of consciousness. The results of such investigations must, therefore, be weighed with caution in relation to the natural history, signs and symptoms of the illness. The overriding importance of clinical observations in this field is thus once again underlined.

3. OLD AGE AND "AFFECTIVE" PSYCHOSIS.

A diagnostic problem frequently causing difficulty is that of differentiating between "functional" psychoses and organic syndromes in old age. Regarded as fortuitous in their incidence in senescence, the former have received little special consideration as problems of old age. However, there are facts on record which suggest some special relationship between old age and the commonest of these psychoses to occur in senescence. If we examine the tables for suicide-rates for different parts of the world (*Mortality Summary for U.S. Registration States: Suicide, 1942*; Schwarz, 1946; *Criminal Statistics for England and Wales, 1937-48*) we observe a steady rise in incidence with advancing age, until a peak is reached usually in the seventh or eighth decade and less often in the sixth. The tables for the U.S.A. (Table I) show that this peak

TABLE I.—Age-Specific Suicide Rates per 100,000 Estimated Population.*

Age.	1940.	1939.	1938.	1935.	1930.	1925.	1920.	1915.	1910.	1900.
All ages	14.4	14.1	15.3	14.3	15.6	12.0	10.2	16.2	15.3	10.2
5-14 years	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.2
15-24 "	6.1	5.9	6.7	7.1	7.5	5.9	6.2	9.8	10.7	6.8
25-34 "	13.5	12.9	14.5	14.3	14.9	12.2	11.5	18.6	17.7	11.2
35-44 "	19.4	18.9	21.0	19.0	22.7	18.0	15.7	23.9	22.4	15.8
45-54 "	27.7	28.2	30.7	28.6	33.0	25.2	20.4	32.2	29.9	19.9
55-64 "	34.4	34.4	37.5	34.9	41.2	30.3	24.2	41.3	37.0	23.5
65-74 "	33.2	34.0	34.4	35.8	42.8	35.8	27.4	39.7	35.3	26.1
75 years and over.	33.3	34.3	34.9	37.1	38.5	31.8	28.8	35.4	38.0	28.2

* United States Bureau of the Census, 1942.

has remained in old age between 1900 and 1940, a period of vast social changes. The suicide-rate among the old has, moreover, remained relatively constant; where fluctuations have occurred they have affected the population as a whole, although the economic plight of the old, in particular, had in this period changed markedly for the worse (Dewhurst *et al.*, 1945). These facts are discrepant with views such as those of Gruhle (1941), who belittles the contribution of mental illness to the suicide rate among the old, and attributes overriding importance to such factors as social isolation, enforced idleness and physical decrepitude. Such views are also out of accord with everyday psychiatric experience, which shows that in contrast to the young, in whom a variety of mental states are associated with attempted suicide, the patient above 60 admitted after trying to take his life is nearly always suffering from a

depressive illness (Mayer-Gross,* 1950; Curran,* 1951; see also below). It seems unlikely that those succeeding in their suicidal attempt are less often suffering from such an illness than those whose failure to achieve their purpose brings them under observation.

A hypothesis put forward by Penrose (1942) would in fact lead us to expect a high incidence of depressive illness in middle and old age. He has pointed out that the age of onset of manic-depressive illness (the commonest manifestation of which is a recurrent depression) is significantly higher in men than in women. The explanation he suggests is that the dominant gene underlying it has had its age of manifestation pushed towards the end of reproductive life, a process to which all dominant genes are subject, owing to the accumulation of genetic modifiers. For there is an advantage from the point of view of natural selection in postponing the onset of a genetically determined illness beyond the end of reproductive life. The greater age of male depressives would thus be due to their longer fertility. This hypothesis offers an explanation for a curious feature of the suicide tables from different racial and national groups, which must otherwise remain an enigma. The peaks for suicide in women in the Swiss tables as well as those for different racial groups in U.S.A. (Table II)

TABLE II.—*Age-Specific Suicide Rates per 100,000 of Enumerated Population by Sex and Race, 1940.**

Sex and race	All ages.	5-14 years.	15-24 years.	25-34 years.	35-44 years.	45-54 years.	55-64 years.	65-74 years.	75 years and over.
Total . . .	14.4	0.2	6.1	13.5	19.4	27.7	34.4	33.2	33.3
Male . . .	21.9	0.4	8.4	19.1	28.2	41.6	55.5	54.7	61.7
Female . . .	6.8	0.1	3.8	8.1	10.6	13.1	12.3	12.1	8.3
White . . .	15.5	0.2	6.4	14.2	20.8	29.4	36.4	35.3	35.2
Male . . .	23.5	0.4	8.8	19.9	30.1	44.1	58.8	58.2	65.2
Female . . .	7.3	0.1	3.9	8.6	11.5	14.0	13.1	12.9	8.7
Negro . . .	4.0	0.2	3.5	6.5	6.2	7.6	6.6	5.9	4.5
Male . . .	6.2	0.4	4.2	10.1	9.9	12.4	11.3	9.3	6.9
Female . . .	2.0	0	2.8	3.2	2.8	2.8	1.5	2.2	2.4
Other races . . .	18.0	0.8	18.8	26.6	18.9	43.0	30.9	47.3	14.2
Male . . .	25.6	1.6	22.3	34.4	22.9	57.8	43.6	72.7	24.7
Female . . .	7.4	0	14.6	12.5	11.1	15.4	0	0	0

* United States Bureau of the Census, 1942.

occur at an earlier age than those for men. Now it is unlikely that these peaks are to be wholly explained in terms of the process of sexual involution. For if there is such a thing as a male climacteric, it does not occur above the age of 75, as does the summit of the curve for suicide among American whites. A difference in the average age of onset of affective disorder in males and females for the reasons suggested by Penrose would, on the other hand, provide a simple explanation for the discrepancy.†

* Personal communication.

† Needless to say, much more research is required into suicide statistics. The interpretations offered here can only be tentative, and are reproduced in the hope that they will stimulate such research, and also because they were among the data that prompted our investigation. In the previous paragraph, it is not, of course, argued that social factors play no part, but that it is through their role in the precipitation of depressive psychoses that they contribute to the causation of suicide in the old.

4. A STUDY OF CASE MATERIAL.

We have chosen to quote such facts hinting at some special association between old age and depressive illness because statistics from some countries (*Patients in Mental Institutions*, 1940 ; *Ann. Rep. N.Y. St. Dept. Ment. Hyg. Albany*, 1942) would lead one to suppose that "functional" psychosis is a rarity above the age of 65. Yet apart from the suggestions offered by the high suicide rates among the old, there are many recent reports of the favourable response to treatment of mental disease in senescence (Evans, 1943 ; Mayer-Gross, 1945 ; Wilbur and Fortes, 1947) to encourage a suspicion that they are more common than is generally supposed. We have, therefore, begun an inquiry into the relative incidence of the different psychiatric disorders in old age.

A detailed study was made of the case-records of the 150 patients over 60 admitted to Graylingwell Hospital during 1948. Subsequently each discharged patient was followed up by letter or a visit by a psychiatric social worker. A diagnosis was arrived at on the basis of the recorded clinical findings alone in most cases ; the results of psychometric investigations were available only in a small proportion. We made our own assessment of each case from the available data, and our final diagnosis did not necessarily correspond with that arrived at by the psychiatrist originally in charge of the case.

From previous clinical observations we had expected that the cases would fall into three principal groups ; those with evidence of progressive dementia with a variable degree of confusion and paranoid colouring (senile psychosis), those with affective disorder mostly of a depressive kind (affective psychosis), and those in which these two clinical states were combined in varying degrees. The other categories, for purposes of classification, were arteriosclerotic psychosis, schizophrenia and confusion. This last category was for cases in which confusion was not complicating one of the disorders already mentioned.

The following points have emerged from this investigation :

(1) The diagnostic grouping and age distribution of 150 cases is shown in Table III. It will be seen that affective psychosis with 81 cases accounted for more than half, or 54 per cent. of the total case material. When 7 cases of mania were excluded, 74 or almost 50 per cent. of the total number were cases of depressive illness. Even if the 60-64 age-group was omitted, depression represented the largest single clinical group. The next largest group was senile psychosis with 36 cases (24 per cent.).

(2) Our material fell into sharply defined groups. Thus there was a clear line of demarcation between affective disorder and senile psychosis ; it is to these two numerically predominant disorders that our comments will be mainly directed in this paper. On the one hand were diseases of clearly defined onset in patients with no evidence in their history of failing adjustment to the demands of their daily life previous to the presenting illness. On the other were those with insidious onset and a history of gradually progressive failure at their work, routine activities, or both. Ignoring the seven cases of mania, we had in the first group 74 patients with positive symptoms of depression, retardation,

TABLE III.—*Diagnostic Grouping and Age Distribution of 150 Patients admitted in 1948.*

Age.	Sex.	Affective psychosis	Schizophrenia.	Senile psychosis	Arterio-sclerotic psychosis	Confusion*	Total.
60-64	M.	11	—	—	2	1	14
	F.	18	3	1	1	6	29
65-69	M.	7	—	—	1	—	8
	F.	19	2	1	—	2	24
70-74	M.	6	2	2	—	2	12
	F.	9	5	7	1	—	22
75-79	M.	4	—	5	1	1	11
	F.	5	—	11	—	1	17
80-84	M.	1	—	1	—	1	3
	F.	—	—	7	1	—	8
85-89	M.	1	—	—	—	—	1
	F.	—	—	1	—	—	1
Totals		81 (54%)	12 (8%)	36 (24%)	7 (5%)	14 (9%)	150

* This refers to cases other than those in which confusion occurred as a complication of one of the other disorders listed on the table.

self-reproach, and, in some cases, nihilistic, somatic or paranoid delusions, in tune with the affective disturbance. In the other group were 36 patients predominantly with negative symptoms of failing memory, deteriorated habits, and a more variable, transient or fluctuating paranoid element. Confusion, with disorientation, failure of grasp, impairment of memory, restlessness and hallucinations, was common and the usual cause of hospital admission in the latter (28 of 36 cases), rare in the former (3 of 81 cases). The overlap between these two principal groups in our clinical material was insignificant. Only in one case of predominantly affective symptomatology was there some suggestion of progressive intellectual impairment. In one case with dementia as its most prominent feature there was some depressive colouring. We therefore decided to dispense with a third provisional group for cases with symptomatology combining both types of clinical picture, and to inquire whether the sharp differentiation we had made was validated or otherwise by the natural history of the cases in the two groups.

(3) It may be rightly objected that such analysis of case-records lends itself to subjective verdicts. Our follow-up studies, however, show that we were probably dealing, in a high proportion of cases, on the one hand essentially with illness having the natural history of affective disorder; on the other with a disease pursuing the progressive and often fatal course of organic disease of the nervous system in old age. Table IV shows that 6 months after admission 46 (56 per cent.) cases of affective disorder were out of hospital, while 5 (6 per cent.) had died. Of patients with senile psychosis, 5 patients (14 per cent.) were discharged and 19 (53 per cent.) had died. On 31 March, 1951 (Table V), the figures were 54 (67 per cent.) discharged, 13 (16 per cent.) dead and 14 (17 per cent.) in-patients among the affective disorders, and 5 (14 per cent.)

TABLE IV.—*Status of 150 Patients, according to Diagnosis, 6 months after admission.*

Diagnosis.	Sex	Discharged.	In-patient.	Dead.	Totals.
Affective psychosis	M.	15	12	3	30
	F.	31	18	2	51
Schizophrenia	M.	—	1	1	2
	F.	3	7	—	10
Senile psychosis	M.	1	1	6	8
	F.	4	11	13	28
Arteriosclerotic	M.	1	1	2	4
	F.	1	2	—	3
Confusion	M.	2	2	1	5
	F.	3	1	5	9
Totals	.	61 (41%)	56 (37%)	33 (22%)	150

TABLE V.—*Status of 150 Patients admitted during 1948, on 31st March, 1951, according to Diagnosis.*

Diagnosis.	Sex.	Discharged.	In-patient.	Dead.	Total.
Affective psychosis	M.	18	7	5	30
	F.	36	7	8	51
Schizophrenia	M.	—	—	2	2
	F.	2	7	1	10
Senile psychosis	M.	1	—	7	8
	F.	4	3	21	28
Arteriosclerotic psychosis	M.	1	—	3	4
	F.	1	1	1	3
Confusion	M.	3	—	2	5
	F.	4	—	5	9
Totals	.	70 (47%)	25 (17%)	55 (37%)	150

discharged, 28 (78 per cent.) dead and 3 (8 per cent.) in-patients among the senile psychoses. (It is interesting to observe also that half the cases of confusion, 2 of 12 cases of schizophrenia and 2 of 7 cases of arteriosclerotic psychosis had also been discharged by this date.) Table VI shows that these differences are not to be accounted for in terms of differences of age between the two groups. Within each age-group containing adequate numbers there is a large discrepancy in the proportion of dead and discharged in the two disorders. In illustration we may quote the number of 13 out of 24 cases of affective disorder between ages 70-79 discharged with 8 deaths in hospital, in contrast to the 21 out of 25 cases of senile psychosis who died in hospital and the one case discharged.

In a follow-up study by letter or visit* by psychiatric social worker we

* Seventy follow-up letters were sent, 41 replies received and the homes of 28 patients visited.

TABLE VI.—*Status on 31 March, 1950, of Cases with Affective Psychosis and Senile Psychosis, according to Age.*

Age-group	Diagnosis.	Discharged.	In-patient.	Dead.	Total.
60-64	Affective psychosis .	19	7	2	28
	Senile psychosis .	1	—	—	1
65-69	Affective psychosis .	20	4	2	26
	Senile psychosis .	—	—	1	1
70-74	Affective psychosis .	9	3	3	15
	Senile psychosis .	1	—	8	9
75-79	Affective psychosis .	4	—	5	9
	Senile psychosis .	—	3	13	16
80-84	Affective psychosis .	—	—	1	1
	Senile psychosis .	3	—	5	8
85-89	Affective psychosis .	1	—	—	1
	Senile psychosis .	—	—	1	1

TABLE VII.—*Status of 70 Discharged Patients (admitted during 1948) on 30 April, 1951.*

Diagnosis.	Sex.	Social recovery.	Relapsed.	Dead.	Not known.	Total.
Affective psychosis	M.	13	1	3	1	18
	F.	24	6	3	3	36
Schizophrenia	M.	—	—	—	—	—
	F.	1	—	—	1	2
Senile psychosis	M.	—	—	1	—	1
	F.	—	—	3	1	4
Arteriosclerosis	M.	—	1	—	—	1
	F.	1	—	—	—	1
Confusion	M.	2	—	1	—	3
	F.	3	1	—	—	4
Totals	.	44	9	11	6	70

have been able to trace the outcome in 64 of the 70 discharged cases (Table VII). It will be seen that 37 of the cases of affective disorder maintain a social recovery, 7 have relapsed, while a further 6 have died. In addition to the 37 cases who remain well out of hospital, 6 of the 14 in-patients with affective disorder have remitted. One of these has had a pre-frontal leucotomy, and this patient as well as two other remissions will be discharged in the near future. In 3 other in-patients discharge is prevented by unfavourable social circumstances. Thus of the total of 81 patients admitted in 1948, with affective psychosis, 43 (53 per cent.) have recovered, 19 (23 per cent.) have died, 8 (10 per cent.) are ill in hospital, 7 (9 per cent.) have relapsed after discharge, while 4 (5 per cent.) patients are untraced. These figures may be compared with 32 (89 per cent.) out of 36 dead, 3 (8 per cent.) deteriorating in-patients and one patient (3 per cent.) untraced among the cases with senile psychosis. This latter disorder is

thus one which proves fatal in the great majority of cases within two to three years. On the other hand, more than half the cases of the disorder we have called affective psychosis may be expected to be alive and well after the same interval, while less than a quarter are dead. The discrepancies may be partly attributable to differences in age, since the senile psychotics were on the whole older, but must to a large extent be attributed, as we have shown above (Table VI), to differences in the course pursued by the two disorders. The mortality of 23 per cent. among the affective psychotics seems to be high until it is remembered that more than 60 per cent were over 65 years of age on admission (Table III). The figures that have been quoted for affective psychosis do not adequately represent the number in which a sustained remission was obtained. In fact, 57 of the 81 patients have been out of hospital for periods of six months or longer, while in a further 4 (now in relapse), who have been in hospital continuously since admission, remissions of over six months have been recorded.

(4) The individual case histories have not provided evidence for any significant overlap between the two main clinical syndromes, affective psychosis and senile psychosis. Cases diagnosed "affective psychosis" on admission might, it could be held, have exhibited this picture as an early manifestation in the process of progressive cerebral degeneration. However, of the 14 in-patients with affective psychosis whom we have been able to study in detail, there is only one pursuing the gradually dementing course of senile psychosis, and her condition is probably due to carbon monoxide poisoning following a suicidal attempt. In one of the patients remaining alive outside hospital our follow-up studies suggested that dementia might have supervened.* In a few of the cases that have died outside hospital since discharge our information is inadequate for a definite opinion to be expressed about the course pursued. There is information from another source suggesting that overlap between the two syndromes is not very common. With the exception of one case of senile psychosis with depressive colouring (already referred to), no patient admitted to hospital with dementia of some duration had a history of affective disorder at an earlier stage, nor did any patient with senile psychosis develop such a disorder while in hospital or, as far as we could determine, following discharge. It could be objected that our material is unrepresentative, but there are reasons for supposing that it is not radically different from that dealt with at many other centres which have published results (*vide infra*). The literature certainly suggests more overlap than we have found. We would, however, suggest that such overlap between affective psychosis and senile psychosis may be due to the fortuitous association of two distinct, though relatively common, disease processes. Our findings offer a similar suggestion with respect to affective and arteriosclerotic psychosis, though, in view of the small number of cases of the latter, it can be no more than a suggestion. A solitary case of overlap between these two conditions has been another of the 14 in-patients originally admitted as affective disorder. This patient, originally a typical depression, has had a cerebro-vascular accident and is now disorientated, emotionally labile, incontinent and ataxic.

* The other depressed patient in whom dementia was suspected on admission (Section 4, para. 2) was aged 79. He was considered too old for E.C.T. and died 4 months later of pneumonia. Depressive features remained to the end.

(5) A number of distinctive clinical features of depressive illness at this time of life are worthy of mention. Apathy was very common in our material, especially in long-standing, untreated cases. Hypochondriacal and paranoid symptoms were more frequent than in younger age-groups. Where they were prominent, results were less favourable than in other cases. Apparently neurotic symptoms commencing for the first time in old age were often sudden in onset, and proved, by their dramatic response to treatment, to have been predominantly endogenous in origin. Another feature which led to difficulties in diagnosis was the occurrence of confusion in the acute stage of three cases of affective disorder. This subsided, to leave behind the typical picture of depressive illness. Twelve of the 150 patients had made a clear-cut attempt at suicide; each was suffering from an endogenous depression.

(6) There were 12 schizophrenics in this case material. In each case the disorder had started after the age of 60 and was paraphrenic in character. Paranoid symptoms were seen in three quite distinct types of disorder in this material:

(a) Paranoid delusions occurring in depressive illness. These were always in harmony with the affective state, and could be interpreted as projections of ideas of guilt and unworthiness and tendencies to self-castigation.

(b) Delusions associated with senile psychosis. These seemed to arise out of the patients' failure of grasp and feeble contact with the environment. They were characteristically transient, non-systematized and ever-changing in character.

(c) Paraphrenic delusions which were prominent in each of the 12 cases in this group. They occurred in each case in the setting of a well-preserved intellect and personality, were often "primary" in character, and were usually associated with the passivity failings or other volitional disturbances and hallucinations in clear consciousness pathognomonic of schizophrenia.

These facts are, of course, well known. Our emphasis upon them is only prompted by the fact that ambiguous terms, such as "senile paranoia," have gained a certain currency in recent years.

(7) When strict criteria were applied, arteriosclerotic psychosis was found to represent only a small proportion of the cases. Cases pursuing a fluctuating course, with cerebro-vascular symptoms and a patchy deterioration of personality with relatively good preservation of insight, added up to seven in number. However, many cases of this disease commence before 60.

(8) The absence of pre-senile dementia might likewise have been due to the lower limit of age being 60. Age is not, of course, the only criterion in diagnosis, but we found no cases with the classical parietal lobe syndrome of Alzheimer, frontal lobe signs of symptoms of Pick's disease, the composite symptomatology of Jakob-Creutzfeldt disease, or any cases of dementia pursuing a course suggesting a rapid process of cortical atrophy. The only cases with epilepsy were clear-cut examples of arteriosclerotic dementia.

(9) Table VIII shows the conditions which were complicated by confusion

TABLE VIII.—*Diagnostic Grouping of Patients showing Confusion and their status six months after admission.*

Aetiology.	Sex.	Discharged.	In-patient.	Dead.	Total.
Senile psychosis . . .	M. .	1 .	1 .	4 .	6
	F. .	2 .	6 .	14 .	22
Arteriosclerotic psy- chosis	M. .	— .	— .	1 .	1
	F. .	— .	2 .	— .	2
Affective psychosis . .	M. .	— .	— .	1 .	1
	F. .	— .	— .	2 .	2
Schizophrenia . . .	M. .	— .	— .	— .	—
	F. .	— .	1 .	— .	1
Non-specific . . .	M. .	1 .	1 .	1 .	3
	F. .	2 .	— .	— .	2
Associated with alcohol	M. .	1 .	1 .	— .	2
	F. .	— .	— .	— .	—
Associated with acute or extensive physical disease	M. .	— .	— .	— .	—
	F. .	— .	— .	5 .	5
Epileptic	F. .	1 .	— .	— .	1
Following upon heavy sedation	F. .	1 .	— .	— .	1
Totals		9 .	12 .	28 .	49

in this material, the number of cases in each diagnostic group and the outcome of the cases in each group six months after admission. It will be seen that there were 28 cases of senile psychosis who were confused on admission, and that 18 of these were dead at the end of six months. Confusion would thus appear to be a fatal complication in this disorder in a majority of cases. Every one of the five cases of confusion occurring as a complication of physical disease had died in the six months. This is in accord with the general clinical impression that confusion tends to be a terminal complication in such cases.

We should like finally to draw attention to the small group of non-specific confusions. These were cases in which there was no clear-out evidence for the complication being merely an episode in the course of senile or arteriosclerotic psychosis. There may, of course, have been unidentified toxic factors or vitamin deficiencies at work, although recovery occurred in three of five cases without specific treatment. The separation of these cases in a distinct group would appear to have been justified by their course. Three of the 5 cases were discharged, and our follow-up studies have shown them all to be well; they constitute 3 of the 5 cases of confusion classified under "social recovery" in Table VII. The old would appear to be especially prone to develop confusional states, and there is little justification in the present state of our knowledge, as Wexberg (1946) and Robinson (1946) have pointed out, for attributing the condition in all cases to a latent senile or arteriosclerotic psychosis or, for that matter, to vitamin deficiency. The benign character of some of these cases of confusion deserves greater emphasis.

(5) DISCUSSION.

The hospital from which these figures were derived is in a rural district and near a number of country towns and seaside resorts, with a relatively high proportion of middle-class and professional people. Since, according to Faris and Dunham (1939), the incidence of old age mental disorder is highest in urban districts, the clinical material might not be representative of that obtaining in the country as a whole. The proportion of functional psychoses might, for example, be disproportionately large. On the other hand, this must be counter-balanced to some extent by the fact that the hospital provides a comprehensive psychiatric service; there is no observation ward in the region which it serves. The number of commonly fatal cases of acute confusion in senile dementia and serious physical disease, which may be expected among admissions to an ordinary mental hospital, is thus probably exaggerated. Moreover, average figures for 7 hospitals obtained recently by Cook and Dax (1951) show some agreement with our figures for discharges and deaths when an allowance is made for our longer follow-up period and their slightly older age-group. They found 38 per cent. dead and 42 per cent. discharged in 2 years as compared with 39 per cent. dead and 45 per cent. discharged within 2 to 3½ years in our material. The suggestion is that the clinical material we were studying was not essentially dissimilar. Clow's figure of 64.9 per cent. of functional psychoses corresponds almost exactly with our own of 62 per cent., but related to a hospital dealing with higher income groups. Post's (1951) figures for cases admitted to an observation ward show, as would be expected, a much higher death-rate and smaller proportion of discharges.

Some of the available statistics from the U.S.A.,* however, suggest an overwhelming preponderance of senile and arteriosclerotic psychosis as compared with affective disorder. Thus the rate of first admissions with senile psychosis in the age groups 60-64, 65-69 and 70 years and over in 1942 is said to have been 11.7, 44.5 and 285.8 respectively per 100,000 of the population of the same age; the figures for arteriosclerotic psychosis were 100.9, 183.2 and 295.5 respectively in these age-groups. In contrast, the rates for involutional psychosis (which seems to cover all affective psychoses in these age-groups) were 15.7, and 7.6 1.1 per 100,000 of the population of the same age. In other words between the ages 60-64 organic psychosis would appear in 1942 to have been seven times as common as affective psychosis, between 65-69 years 20 times as common, and above 70 years more than 500 times as common. Again in a more limited study of 683 first admissions over the age of 65 Camargo and Preston (1945) found 85 per cent. to be suffering from senile or arteriosclerotic psychosis. Now it is true that first admissions are likely to form a smaller proportion of affective psychoses in old age than of organic psychoses, but the preponderance of the latter in the American figures is probably too great to be wholly explained in this way: more than half of our cases of affective psychosis were first admissions, and the proportion of patients whose first attack had commenced after the age of 60 was well over half. It is possible

* Annual Report of New York State Department of Mental Hygiene, Albany, 1942.

again that affective disorder is less likely to be treated in mental hospitals in the U.S.A. than in this country, but figures for rate of admission of cases of affective psychosis in earlier age-groups in the U.S.A. dispose of this explanation. One cannot help wondering, therefore, whether underlying the American figures there may not be a much wider interpretation of senile and arteriosclerotic psychosis than can be justified on theoretical and practical grounds.

While our findings would appear to have some general relevance, further investigation of clinical material and comparison with the experience of other centres is obviously indicated for a proper evaluation of their significance. Certain points may, however, be stressed even at this stage. The presence of positive and sustained signs and symptoms of affective disturbance calls, in our judgment, for reconsideration of a diagnosis of organic psychosis in old age. Whenever such positive clinical signs are present a considerable degree of recovery, sustained or temporary, may be expected. A failure to make a correct diagnosis may be fraught with dire consequences for an old patient. Depressive illness in the aged takes a terrible toll in death from exhaustion, pneumonia and other intercurrent infections. It need hardly be said that a fatal outcome, after many months or years in hospital with some pre-terminal physical decline and mental confusion, is no confirmation for a diagnosis of organic psychosis. The differential diagnosis between a depressive illness and a senile psychosis can indeed be difficult. A depressed patient may be so retarded and apathetic, wasted, dirty and neglected that a long-established cerebral degeneration seems the most probable cause of his illness. Only a detailed and carefully taken history can provide the clue to the diagnosis, but it may prove impossible to obtain it from the patient, and when, as is often the case, he lives alone there may be no relative to speak with recent knowledge of him. In such circumstances the diagnosis cannot be established with certainty. There is a therapeutic test which will settle any doubt about the presence of a depressive illness; three or four E.C.T. administered within 14 days will produce an unmistakable change in mood, spontaneity and general vitality. There is no evidence to suggest that where a cerebral atrophic process and not an affective psychosis is the underlying cause it is accelerated by such treatment.

Further investigation is urgently required into the pathology of this group of mental disorders. We need information as to the comparative neuropathology of cases that recover and of those whose illness pursues a progressive and irreversible course. One wonders, if we may diverge from our main theme for a moment, whether in seeking for a pathology of organic psychosis in old age we have not been too preoccupied with the cerebral cortex. The core of the syndrome of senile psychosis in its initial stages of development is a selective impairment of recent memory and retention, and faulty location of recent events in time. We have been impressed by the frequency with which this is associated with a fatuous, euphoric affect and superficial alertness to produce what is in effect a Korsakow syndrome. The tendency to confabulation is, as always, proportionate to the amount of initiative. The commonly co-existing paranoid element is variable and ill-systematized; it derives from the failure of memory and lack of grasp. This symptom-complex is seen in a

variety of organic psychiatric states. It appears to be a preformed psychophysiological response, for the picture is the same whether the association is with chronic alcoholism, Wernicke's encephalopathy, anosognosia for physical disease, head injury or senile cerebral atrophy. Now the work of Gamper (1927), Meyer (1944) and others has shown that a hypothalamic lesion, probably in the corpora mammillaria, may be adequate by itself to produce a Korsakow syndrome. It will be remembered, moreover, that E.C.T. tends to produce just this combination of euphoria and selective impairment of recent memory which becomes with excessive dosage the gross amnesia, pathological elation and confabulation of Korsakow's syndrome, with a variable paranoid colouring and tendency to aggressiveness. The importance of this lies in the fact that there is considerable evidence to suggest that the primary and therapeutic effects of E.C.T. are exerted on the diencephalon (Gellhorn, 1943, 1949; Delay, 1946; Roth, 1951). This site of the homeostatic centres of the organism may thus repay further investigation in relation to the organic psychoses of old age.

The facts of most immediate practical importance issuing from our work are the predominance of "functional" psychosis in our clinical material and the sharpness with which they are distinguished from organic psychosis. Their numerical preponderance has revealed this differentiation between depressive illness and senile psychosis in particular, and the benign prognosis of the former illness in the old is a phenomenon of the greatest importance. It suggests that, by the application of modern concepts in the diagnosis, treatment and rehabilitation of old patients, psychiatry may well be able to meet the challenge offered to it by the rising proportion of the aged in the general population.

SUMMARY.

1. The main problems arising in connection with the differential diagnosis of mental disorder in old age are discussed.
2. Evidence from various sources is quoted suggesting some special relationship between old age and depressive illness.
3. A study of the case-records of 150 patients over the age of 60, admitted to a mental hospital in 1948, shows affective psychosis to be the largest clinical group, accounting for 54 per cent. of the cases. Senile psychosis accounted for 24 per cent.
4. Follow-up studies provide some objective validation for the diagnosis attached to the cases in these two principal groups. Thus on 31 March, 1951, almost 90 per cent. of the cases diagnosed senile psychosis were dead. More than half the cases classified as affective psychosis were alive and well; less than a quarter were dead. The discrepancies were marked within each age-group.
5. The natural history of these two disorders suggests little overlap between them. It is suggested that they are distinct nosological entities, and that, where a co-existence of the two types of clinical picture is observed, this may be fortuitous.
6. The sharp distinction between the different types of disorder with paranoid symptoms is emphasized.

7. The diagnostic classification of cases showing confusion is described. Attention is drawn to the usually fatal outcome of confusion complicating extensive physical disease and of the benign prognosis of cases of "non-specific" causation.

8. The significance of the findings is discussed.

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ADRENAL CORTICAL FUNCTION AND RESPONSE TO CONVULSIVE THERAPY IN A CASE OF PERIODIC CATATONIA.

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ANY patient who shows a regularly recurring change of mental state will be of particular interest to the research worker, for in the recurrence, by acting as his own "control," the patient provides the best of all comparisons.

Such a patient, a woman aged 39, provided the basis for this work. Usually sensible and well spoken, she would, about every twenty-first day, become confused and incoherent. Convulsive therapy (E.C.T.) always caused an immediate improvement, and within two or three days she was well again. (Previous experience had established that the confusion had little spontaneous tendency to recover.) As she provided this regular cycle, a systematic investigation was made over several months into those aspects more particularly relevant to the effect of E.C.T. on the adeno-hypophyseal-adrenocortical system, for a previous study (Ashby, 1949) had suggested that E.C.T. might owe its effectiveness to action through this system.

The various investigations will be described later ; first, the patient.

DESCRIPTION OF CASE.

M. M. B— came of a healthy family and passed an uneventful childhood. Her personality was happy, good-natured and friendly. She trained successfully as a nurse, married when 28 and bore two children, one and three years later. When aged 38 she had an attack of confusion, which was soon terminated by E.C.T. The attacks recurred, however, and presently settled into a steady rhythm of 20–25 days. Between the attacks she was quiet and well behaved but was dull and apathetic. Her conversation consisted only of giving answers to direct questions, and she soon tended to return to a simple statement that she wanted to go home. This plea was put forward repeatedly without variation or elaboration, accompanied by a uniform and rather mechanical smile. She was content to knit all day, and made no effort to make social contacts or to take part in any social activity. In these intervals she had no delusions or hallucinations, was correctly orientated for time and place, and possessed a normal memory for events, both recent and remote. Her insight was not complete.

Two specialized psychological tests were applied, each in a lucid interval. The first, a Form/Colour-sorting Test (Goldstein, 1939 ; Weigl, 1941) was applied seven days after a convulsion. It showed her able to classify the material by colour but unable to find any other basis for classification, an

inability considered by Goldstein and Weigl to indicate an impairment of abstract thought. The second, the Rorschach, was applied three days after a convulsion. It was applied in two forms. In the first, the Individual, her responses were confined to naming the cards as "ink splodges" and to naming pure colours. Card VIII initially provoked a colour-naming response, but then a simple animal form was discerned: "that might be a mole, only it's red." Testing the Limits on all the other cards showed that the patient was unable to utilize concepts of Form. The second form, applied the same day as the Individual, was the Harrower-Erickson and Steiner Multiple Choice (Harrower-Erickson, 1945): to this her selected responses did not differ appreciably from those given to the Individual; colour-naming was the most usual. The significance of these responses will be discussed below.

After about three weeks of quiet and apathetic life she would, in a few hours, become surly, irritable, apt not to reply if spoken to, and at meal times would leave much of her food untouched. A few hours later she would be negativistic, mute, and inactive, or confused, resentful, and mumbling. She never became violent, but was often "difficult." Fragmentary delusions were sometimes expressed, and she seemed at times to be aurally hallucinated. Treatment by E.C.T. was then started, and was invariably effective. After the first convulsion she was often completely restored to her former condition; but she usually relapsed during the day, and two or three further convulsions daily might be required to establish her usual, one cannot say "normal," state.

After some months the periodicity became less regular, her mental condition showed less abnormality, and she left hospital, to continue treatment as an out-patient until this too was discontinued. She now lives at home, something of an invalid, but just able to look after herself and to do simple home tasks. The investigations described here occupied the time when the periodicity was well marked.

The diagnosis of her illness is not easily made. A recurrent mania is unlikely, for in each attack there was no over-activity, no flight of ideas, no restlessness, no insomnia. The frequency of three weeks is very short for a manic cycle, though the fully documented case of Klein and Nunn (1945) shows that a cycle as short as seven days is possible. A second possibility is that she conforms to the recently defined "oneirophrenia" of Meduna (1950): her psychosis was benign, she responded well to E.C.T., and she was, as will be shown below, somewhat insensitive to insulin. Clinically the picture was very different: she gave no evidence of any disorder of perception, she showed no dream-like state at any time, and her cyclic variation was not typical of this condition. More likely is the diagnosis of periodic catatonia. Her apathy in the intervals, her poverty of ideation, her flatness of emotion, her lack of insight when remembering events from the reactive phase, her sex, and her phases of mixed excitement and stupor, all support this possibility. In addition, she resembled Lindsay's (1948) cases in her response to E.C.T. On the other hand, 38 years of age is late for the onset, and dementia, except perhaps of the mildest degree, has not developed. Further, the patient was, as will be shown below, markedly vagotonic. In this she was unusual: all Gjessing's

(1938) now classic cases showed sympatheticotonia; and Stokes and Hardwick (1941) noted in their cases that the intervals of stupor were invariably marked by increases in both pulse-rate and blood-pressure. Whether the difference of sex, for all the cases of Gjessing and of Stokes and Hardwick were male, can account for the difference is uncertain, but if the facts are considered as a whole, the diagnosis of "periodic catatonia" seems the most likely.

THE INVESTIGATION.

Our first aim was to see whether information could be obtained about how E.C.T. achieved its effect. Several lines of reasoning suggested that its action on hypothalamus, adeno-hypophysis and adrenal cortex would be of interest. The following investigations were therefore made:

Sugar-active Cortins.

These steroids are of interest for several reasons. The group includes those steroids more particularly active in glucose metabolism; and it is therefore of interest in any patient whose cerebral metabolism might be defective. The group, too, was shown by Ashby (1949) to be the first evoked by E.C.T., a sharp rise in the 24-hour urinary excretion occurring within the first few days after the first convulsion. It is of topical interest, for it includes cortisone (17-hydroxy-11-dehydro-corticosterone); and, though reports conflict, there is some evidence (discussed below) that this substance may, in some conditions, have an effect on the patient's mental state.

The method of assay was as follows: The urine was collected in 24-hour batches, in this case without preservative, as the investigation was conducted in the cooler months. It was acidified to pH 1.0 with methyl violet as indicator, as previous investigation (Ashby, 1949) had shown that in the extraction of these steroids this pH is optimal. It was extracted with one-tenth its volume of chloroform three times, the extracts combined, and any emulsion broken down by centrifugation and, if necessary, by trituration with anhydrous sodium sulphate. The extract was then concentrated by evaporation of the chloroform *in vacuo* from a water bath thermostatically controlled at 50°C. When the volume was reduced to about 10 ml. the concentrated extract was transferred to a separating funnel, and washed repeatedly with 5 ml. lots of N/10 sodium hydroxide until all extractable phenols had been removed. It was then washed three times with 5 ml. lots of water, which were back-extracted with 10 ml. of fresh chloroform, which was returned to the main solution. This was again reduced in volume *in vacuo* at 50°C., transferred quantitatively to a test-tube, and the chloroform removed by evaporation under a stream of dry nitrogen at 50°C. At this stage the dried cortins, kept in the refrigerator, have been found to be stable for at least 14 days.

The next stage in the assay was based on the fact, first used by Reinecke and Kendall (1942), that the adrenalectomized rat, when fasted, rapidly loses glycogen from the liver, and that a class of adrenal steroids—the "sugar-active"—will restore the glycogen content to its normal value. So the

induced glycogen can be used to assay the steroids. We used immature Wistar-strain rats weighing between 35 and 50 gm. because their smaller weight allows a more sensitive test. Under ether anaesthesia they were adrenalectomized by the lumbar route and transferred to a room thermostatically maintained at 70°F. During the first 24 hours after operation their drinking water contained 0.9 per cent. sodium chloride and 5 per cent. glucose; subsequently the glucose was omitted. Food was given freely till the evening of the fourth day, when all was removed. On the morning of the fifth day the cortins were administered. They were dissolved in ethanol, to which was added glucose and water in quantities so that the final solution contained 10 per cent. ethanol, was of volume sufficient to provide seven doses of 0.4 ml. and contained a total of 0.15 gm. of glucose. The latter was added as it had been found (Venning *et al.*, 1946; Ashby, 1949) to improve greatly the sensitivity and accuracy of the assay. At the end of the day, one hour after the last injection, 1 ml. of 5 per cent. sodium amytal was injected intraperitoneally, as this method of killing had been found to avoid certain difficulties caused by neck-breaking. As soon as the animal was anaesthetized, it was weighed, opened, and the liver removed and snipped piecemeal into 20 ml. of 30 per cent. potassium hydroxide that had previously been raised to 100°C. in a boiling water bath. Digestion was continued to completion, with a minimum of one hour. After cooling, the glycogen was precipitated by the addition of 1.1 to 1.2 volumes of ethanol and by heating gently in a water-bath until the liquid just boiled. From this suspension an aliquot was removed and the glycogen separated by centrifugation. It was hydrolyzed by heating with 5 ml. of 0.6 N hydrochloric acid in a boiling water bath for 2½ hours. After neutralization, an aliquot was added to Hagedorn and Jensen's alkaline ferricyanide, which it partially reduced; after the addition of iodide and acetic acid, the liberated iodine was titrated with N/200 sodium thiosulphate. Simple calculation converts the titration volume to the quantity of glycogen originally in the liver, and thus to the quantity of liver-glycogen per 100 gm. of carcass.

There remains the question of how this deposit is related to the quantity of cortins injected. When pure substances are being assayed this question hardly arises: the unknown quantity of the pure substance is administered to one batch of animals in parallel with known quantities of the same pure substance administered to other batches, and as the animals' responses are similar in type, differing only in degree, the relative potencies may be determined by the application of well known statistical methods. Even when the preparations are mixtures, provided that the two preparations are similar in their compositions, then this procedure may still be used. In the present work these conditions do not occur. The group of "urinary cortins," though probably containing some of the adrenal cortical steroids, contains them in unknown proportions. Further, the proportions may well vary from day to day. To use a pure steroid such as corticosterone as standard against a mixed and unknown group would be arbitrary and meaningless. Exactly the same argument applies against the use of a standard mixture, however carefully it be standardized, for its composition will almost certainly

differ, to an unknown extent, from any particular sample. For these reasons it seems better to record simply the primary fact—that the preparation on injection under standardized conditions resulted in the deposition of a certain weight of glycogen (adjusted for the weight of the test animal). Such a form of statement begs no questions and needs no arbitrary assumptions, but retains the factual information yielded by the assay.

Reducing Cortins.

Also estimated daily were the "reducing" cortins, identified by their common power of reducing alkaline ferricyanide, chiefly by their possession of a ketol side-chain at C-17. The group, of course, overlaps to some extent the group of the "sugar-active": among the common members are corticosterone and its 11-dehydro-, 17-hydroxy-, 17-hydroxy-11-dehydro-, and 11-desoxy- derivatives. At the present time exclusive classification of the steroids is not possible, and the division adopted was the best possible under the circumstances.

The extraction described above removed both types of cortins, and the extract was divided into known fractions for the subsequent assay. The part used for assay by reduction was first kept for seven days, since it had been found that some tarry substances difficult to remove were oxidized in this time and interfered less with the analysis. The extract was then dissolved in ethanol, and the reducing power of the solution determined by the method of Hagedorn and Jensen in the usual way. The final values were expressed as the weight of glucose equivalent to the sample in reducing power. This direct way of stating the facts seems preferable to the use of a conversion factor, which, being necessarily single, cannot adequately represent a group of steroids varying both in reducing power and in molecular weight.

17-ketosteroids.

These substances are excreted mostly in conjugated form and can be assayed only after hydrolysis. To 250 ml. of the urine was added one-tenth of its volume of concentrated hydrochloric acid; it was then boiled for ten minutes. After slight cooling, 75 ml. of carbon tetrachloride were added and the mixture re-boiled under a reflux condenser for another twenty. After cooling, the carbon tetrachloride was separated, washed with distilled water, with 10 per cent. sodium hydroxide, and again with water. The solvent was driven off *in vacuo* and the residue taken up in 4 ml. of ethanol. Every few days potassium hydroxide of high purity was dissolved in ethanol, titrated, adjusted to 2.5 N, and kept in a stoppered bottle at 4°C, out of the light. In alcoholic potash, 17-ketosteroids and dinitrobenzene give a red colour, and this was used for the assay. Crystalline androsterone, itself a 17-ketosteroid, was used as standard to calibrate the photoelectric colorimeter.

The assays of cortins and ketosteroids, especially those depending on biological tests, were very time-consuming, restricting what could be done.

By sampling each substance or group of substances intermittently we could have extended our range of investigation; but as we were looking for day-to-day changes associated with the mental changes, which occurred within almost a few hours and were not entirely predictable, we considered it better not to leave gaps. These assays were therefore carried on continuously, but the decision meant that the variety of investigations had to be restricted.

Creatinine.

The urinary concentration of creatinine was also estimated daily, partly as a means of detecting diuresis, and partly because it was wanted in conjunction with the concentration of uric acid, as described below. The method used was the usual formation of its picrate, which was estimated in the photoelectric colorimeter against a standard of pure creatinine.

Uric Acid.

It has been known since the work of Forsham *et al.* (1948) that the excretion of uric acid is markedly increased in the human being after the administration of adrenocorticotrophic hormone (A.C.T.H.). We therefore estimated the concentration of uric acid daily, using the method of Benedict and Franke.

As it has been found (Thorn *et al.*, 1947) that administration of the hormone does not affect the excretion of creatinine, and as the concentration of this substance gives an excellent correction for variations in volume, most workers have preferred to express the excretion of uric acid by the ratio: concentration of uric acid/concentration of creatinine, briefly U/C. Usually 0.3 to 0.4, this ratio rises in the normal person to an average value of 1.2 a few hours after the intramuscular injection of 25 mgm. of A.C.T.H. (Thorn, *et al.*, 1948).

Sensitivity to Adrenaline.

The patient's response to adrenaline was tested throughout under uniform conditions. She remained in bed, unoccupied and undisturbed, for the hour before the test. The systolic and diastolic pressures in the left brachial artery were measured at one-minute intervals. After the base line had been clearly established, adrenaline, 20 μ g. per kgm. of body weight, was injected with a fine and specially sharpened needle. The blood-pressure was then read at one minute intervals for not less than forty minutes.

Since the test interrupted the uniformity of the other observations, it could be applied only intermittently.

Sensitivity to Insulin.

The patient's sensitivity to insulin was measured by the method of Fraser and Smith (1941). Fasting from the previous evening, she was given insulin intravenously 0.1 units per kgm. of body weight. Blood was taken for analysis at half-hourly intervals.

Response to Adrenal Cortical Steroids.

A course of injections of adrenal cortical extract was also given and its effects observed. "Eucortone," 0.5 ml., was given intramuscularly each day for 14 days. That the preparation was potent was established by previous trials of its power to induce glycogen deposition in the adrenalectomized rat.

Psychogalvanic Response.

Since there is some evidence that the psychogalvanic response (P.G.R.) is mediated by and dependent upon, sympathetically-controlled changes in the sweat glands, and as the patient's sympathetic system, as described below, was found to be grossly unresponsive, an examination of the P.G.R. was made daily over 28 days to see whether its changes would throw light on the nature of other changes. The response was tested by the method standardized previously (Ashby and Bassett, 1950). At each session four stimuli were presented—the smell of 2 per cent. ammonia, a flash from a "Photoflood" bulb, a pinch of the ear-lobe with a standard clip, and a touch on the cornea with a wisp of cotton-wool. Each was presented once in actuality and once only as a threat. All eight were presented at each session, the order of presentation being determined from a table of random numbers. As we were not interested in the distinctions between the sensory modes, we used as scores the average of the four deviations caused by the real stimuli and the similar average of those caused by the threats. The first average gave some measure of the patient's responsiveness to direct sensory stimulation, while the second gave some measure of her responsiveness to purely symbolic presentation.

Other, minor, investigations will be described in their context. In view of the diagnosis of periodic catatonia, it would have been interesting to include investigations of the nitrogen balance; but to add these to the other investigations was beyond our resources.

This completes the account of what was done; next to be described is what was found. The results are given mainly in Fig. 1, which shows how the variables changed during the several cycles of the $4\frac{1}{2}$ months' observation. One complication should be noticed. The periods of excitement are almost necessarily co-extensive with those of treatment by E.C.T., for treatment could not be withheld when it was required. The two variables, as factors affecting the results, are therefore, in Fisher's terminology, confounded; and any deductions must be drawn with corresponding caution. The complication will be referred to below when necessary.

EXCRETIONS OF ADRENAL CORTICAL STEROIDS.

The first aim of the investigation was to discover whether the outputs of sugar-active cortins, of reducing cortins and of 17-ketosteroids bore any relation to the phases of excitement and treatment. The information is given in Fig. 1, but the results are rather too dispersed for ready inspection. A fresh table

was therefore drawn up combining the results by super-position: all those days were brought together which occurred on a first day of excitement, and so on. The new table showed more clearly the trend than the minor details of day-to-day fluctuation. The averages are given in the Table. The reducing

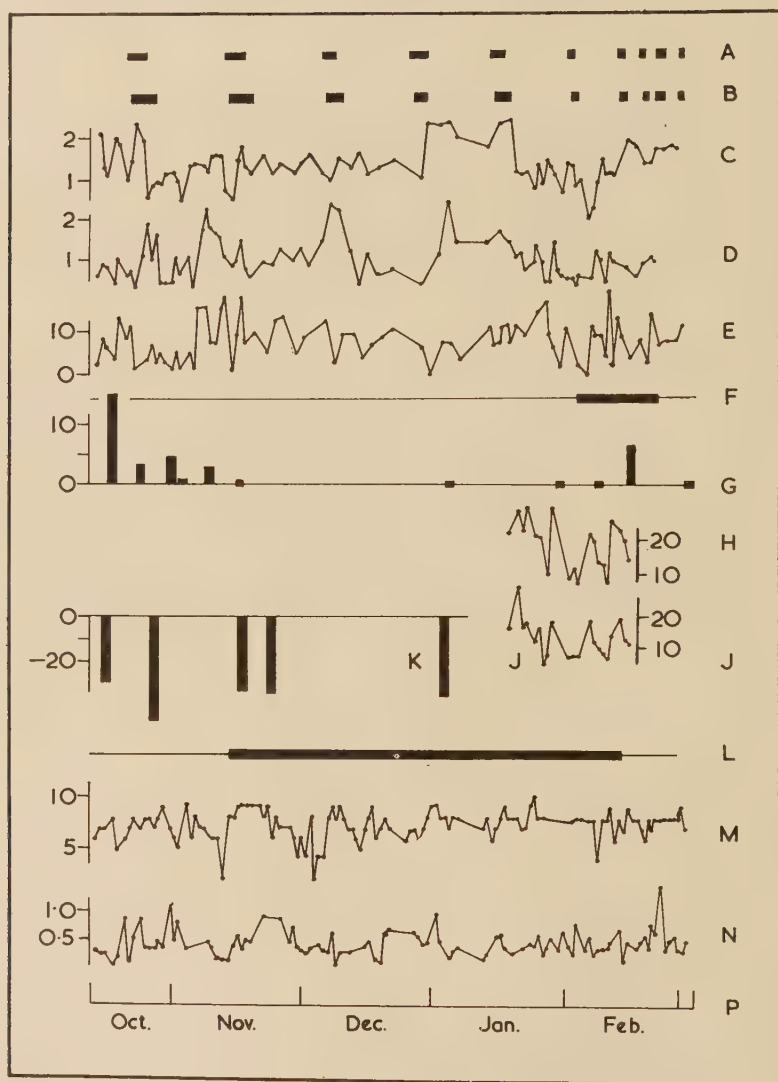


FIG. 1.—The results of the investigation. Observations made on the same day lie on the same vertical line. Time goes from left to right. The variables are:—*A*, phases of excitement, marked black. *B*, periods of E.C.T., marked black. *C*, excretion of sugar-active cortins, shown as $\log_{10}$ (mgm. glycogen/100 gm. rat/24 hours). *D*, excretion of reducing cortins in mgm. glucose equivalent per 24 hours. *E*, excretion of 17-ketosteroids in mgm. per 24 hours. *F*, period of administration of adrenal cortical extract, marked black. *G*, adrenaline sensitivity, shown as average rise in systolic B.P. (mm. Hg) over 20 minutes. *H*, P.G.R. to real stimuli. *J*, P.G.R. to threatened stimuli. *K*, insulin sensitivity, shown as percentage fall in blood glucose at 30 minutes after injection. *L*, interval during which nocturnal sedative was given. *M*, hours of sleep. *N*, U/C ratio. *P*, time.

TABLE I.—*Results from the Excited Phases Superimposed.*

Each number is the average of several results. The day on which the first noticeable excitement occurred is marked "0"; those numbered negatively preceded it. The sugar-active cortins are given as "mgm. glycogen/100 gm. rat"; the reducing cortins as "mgm. glucose equivalent"; and the 17-ketosteroids as mgm.; all per 24 hours.

Days.									
	-4.	-3.	-2.	-1.	0.	+1.	+2.	+3.	+4.
Sugar-active cortins	16	41	41	32	16	24	63	74	42
Reducing cortins	1.3	0.9	1.0	1.2	0.8	0.6	1.0	0.9	1.3
17-ketosteroids	12.2	7.6	7.9	13.0	8.3	10.6	3.9	5.4	9.0

cortins and the 17-ketosteroids show little more than the fluctuations of experimental error, but the sugar-active cortins (Fig. 2) show some tendency to rise at about the second and third day. In the case of these steroids, we can be fairly sure that the effect is due to the E.C.T.; for it has already been shown

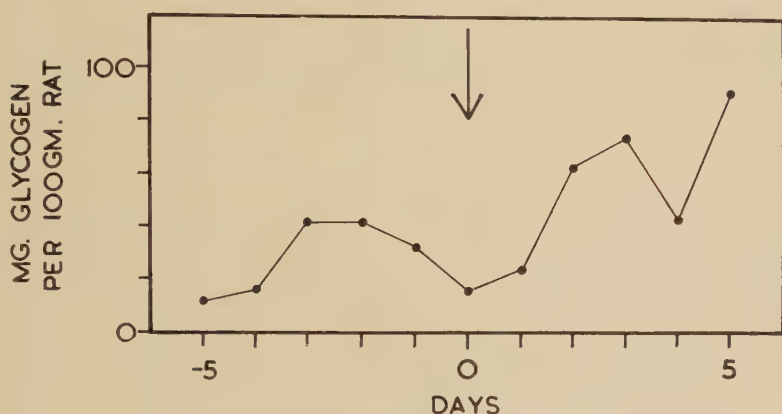


FIG. 2.—Changes in the urinary excretion of sugar-active cortins, measured by the glycogenic response of the adrenalectomized rat, over the onset of excitement and the commencement of E.C.T., which is marked by the arrow.

(Ashby, 1949) that the usual effect of E.C.T. is to cause an "outpouring" of adrenal cortical steroids, especially the sugar-active, within the first few days after the first convulsion. In this patient the reaction is sluggish and, in the protocols, obscured by other disturbances. The fact that the 17-ketosteroids show no particular change after E.C.T. confirms the previous observation that this treatment typically causes no change in their excretion.

To study the interrelations of the steroids more closely, the daily outputs of the three classes of steroids were correlated over the whole investigation. Between the sugar-active and the reducing cortins the product-moment correlation was $+0.179$, which is not statistically significant; neither is that between the sugar-active cortins and the 17-ketosteroids: $+0.016$. But that between the reducing cortins and the 17-ketosteroids was $+0.339$, which is statistically significant with $P = 0.02$. The 24-hour excretions of the two classes of steroids tend therefore, as the sign is positive, to rise and fall together. The linkage cannot be due to the presence of common steroids, for the ketol group of the one and the ketonic oxygen of the other cannot both occupy C-17.

The correlation is therefore probably due to their being each an indication of the activity of the adrenal cortex.

The converse study was made of seeing to what extent the patient's behaviour, clinical and metabolic, would be influenced by the administration of adrenal cortical steroids. No clinical effect could be observed, and its effect on the periodicity of her symptoms was small or absent. (It had another effect, however, which will be referred to later.) No detectable quantity of the administered steroids could be recovered from the urine, for the excretion-rates showed no significant increase during the administration. This is not surprising, for Vogt (1943) showed how rapidly the adrenal steroids disappear after their entry to the circulation; and other workers, using far larger quantities, could recover from the urine only a small fraction of the injected steroids; thus Venning *et al.* (1944) recovered less than one-tenth, Talbot *et al.* (1947) recovered nothing, and Dorfmann *et al.* (1944) recovered only a trace.

The results, then, show firstly that the application of E.C.T. tended to be associated with a rise in the excretion of the sugar-active cortins.

U/C RATIO.

The U/C ratio (urinary uric acid/urinary creatinine) was found to be significantly affected by the application of E.C.T. On the days when treatment was given, the mean value (0.51) exceeded that of the other days (0.39) by 0.12, which, though small, is statistically significant ($P = 0.02$), and which is also, it will be noticed, in the expected direction. Altschule *et al.* (1949) had observed the same effect, finding that the ratio is raised maximally at 4.5 hours after convulsion, rising on the average from 0.45 to 0.64. The fact that our patient's increase is somewhat less than his is explained by the fact that Altschule studied hourly specimens which showed the change individually, while we studied a 24-hour specimen.

Our value can be used in conjunction with the data of Thorn *et al.* (1948) to get an estimate of the amount of A.C.T.H. secreted by our patient. The estimate is admittedly of low accuracy, but is useful in giving an indication of the effect's order of magnitude. Thorn's data show how the U/C ratio varied hour by hour after a single injection of 25 mgm. of A.C.T.H. Our data show how the U/C ratio was altered in the whole 24-hour specimen. So our result is an integral of his. The simplest way to make them comparable is to convert Thorn's result to what it would have been had all his patient's specimens been combined to form one 24-hour specimen. We want, in fact, to compare our 0.12 with the integral

$$\frac{1}{24} \int_0^{24} \left(\frac{U}{C} - R \right) dt,$$

where t is the time in hours, R is the resting value of U/C in Thorn's case (0.30), and U/C is a function of the time, tabulated by Thorn. After numerical integration the expression proves to be 0.13, which we can compare

with our patient's 0.12. The smallness of the difference suggests that our patient's secretion of A.C.T.H. may be estimated very approximately at about 25 mgm.

In the rat, pig and human being, the dried pituitary is about one-fifth A.C.T.H. (Burns *et al.*, 1949), and under severe stress about one-half of the hormone is secreted; it follows that under severe stress the human pituitary will secrete about 10 mgm. This figure emphasizes the approximate nature of our estimate of 25 mgm. Though probably too high, it suggests tentatively that E.C.T. may be a fairly potent stimulus to A.C.T.H. secretion, at least in this patient.

The administration of adrenal cortical steroids caused no significant change in the U/C ratio.

Since the U/C ratio and the excretions of cortins and 17-ketosteroids tend to be affected by common variables, the correlations were calculated between them in pairs. The product-moment correlations between U/C on the one hand and, on the other, the concentrations of sugar-active cortins, reducing cortins, and 17-ketosteroids were + 0.050, - 0.174, and - 0.224 respectively. As none is significant at the 5 per cent. level, no comment is needed.

PSYCHOGALVANIC RESPONSE.

The P.G.R. was related to the outputs of steroids by calculation of the product-moment correlations, to see whether the day-to-day variations in the magnitude of response tended to be associated with larger or smaller excretions of steroids. Six correlations were computed: those of the response to real or threatened stimuli with the excretions of the three types of steroid. All were found to be non-significant. On the other hand, the administration of adrenal cortical steroids may have had some slight effect. When the responses before were compared with those during its administration, the reactions to the real stimuli were found to be reduced in the ratio 100:72, a change just significant statistically ($P = 0.04$). I am not inclined to stress the point; for when, as in this paper, a number of results have to be tested for significance, it is to be expected that about one in twenty will pass the 5 per cent. level of significance although no true effect is present. As a final test, the correlation was calculated between the responses and the U C ratio, but nothing significant was found.

SLEEP.

Another line of investigation into the activities of the hypothalamic centres is given by observations on sleep. Although the precise distribution and function of these "centres" are still obscure, that some regions of the hypothalamus play an important part in determining the states of "sleep" and "vigilance" is indubitable. Of particular interest in view of our patient's insensitivity to adrenaline (described below) is the work of Nauta (1946), who, having provided confirmatory evidence that a caudal centre generates the "alert" state, which in sleep is inhibited by impulses from an anteriorly-placed "sleep" centre, went on to show that these centres are topographically identical with

those determining autonomic balance. Throughout the investigation, therefore, the patient's hours of sleep were specially observed and recorded. A complication must, however, be mentioned. Through two-thirds of the investigation she received a uniform sedative (soluble barbitone, gr. $7\frac{1}{2}$ at 8 p.m.). This increased somewhat the average level of somnolence and made the two parts of the investigation not directly comparable; but the effects of the disturbance can be eliminated by calculating all results separately for the two periods, examining them for evidence of significant difference, and, if none is found, combining them to form the final result. This method was followed in all tests which might have shown disturbance, but none was found.

To test for association between variations in the hours slept and in the amounts of cortins and steroids excreted, the product-moment correlations were calculated for the three classes of steroids. "Hours of sleep" correlated with sugar-active cortins to the extent of $+0.119$, with reducing cortins $+0.004$, and with 17-ketosteroids -0.115 . None is significant statistically.

The administration of adrenal cortical steroids was tested for its effect on the hours of sleep; no effect could be observed. The correlations between hours of sleep and other variables were: U/C ratio, $+0.165$; P.G.R., real stimuli, $+0.019$; P.G.R., threat, -0.051 . None is statistically significant. Observation of the hours of sleep has proved of little value in this patient.

SENSITIVITY TO ADRENALINE.

When the results were reviewed, it was found that after the injection of adrenaline the patient's diastolic pressure remained always unaffected, so attention was focussed on the systolic. Inspection of the protocols suggested that the patient's response in the interval between the injection and 20 minutes later was not homologous with that occurring subsequently. It was therefore decided to take as the response the average rise in systolic pressure over the first 20 minutes. This average was found by graphing the pressure as ordinate against time as abscissa, integrating with Amsler's planimeter the area bounded by the curve, the time-axis, and the 20-minute ordinate, and then finding the mean ordinate.

When the results, shown in Fig. 1, are reviewed, it is clear that the first response was the largest—an average rise of 15.1 mm. (A normal subject tested as control gave an average rise of 29.4 mm.). In the later tests the responses were either negligible or actually negative, in which case the reactive systems overpowered the direct response. In general, her insensitivity to adrenaline was one of her outstanding pathophysiological characteristics.

The effect of E.C.T. on her insensitivity can be deduced by comparing her responses when she was having treatment with those during the quiet phases. In contrast to the patients of Funkenstein *et al.* (1948), who became more sensitive to adrenaline after E.C.T., our patient showed no change. There was, in fact, a striking contrast, when given E.C.T., between her immediate improvement mentally and her unchanging insensitivity to adrenaline.

For purposes of comparison, her sensitivity was tested to other sympathetico-mimetic and related substances. Amphetamine was tested three times

(at doses of 5, 10, and 10 mgm.) and gave average responses of $+2.6$, $+6.0$, and $+4.9$ mm; ephedrine (75 mgm.), tested twice, gave $+4.8$ and -0.7 ; nikethamide (1.7 ml.), tested twice, gave -2.2 and $+0.6$; *d*-N-methylamphetamine (10 mgm.), tested twice, gave -0.3 and $+1.1$; and *iso*-propyl-nor-adrenaline (20 mgm.), tested twice, gave $+7.4$ and $+1.0$. Only the latter, and perhaps amphetamine, caused any significant response.

In view of the observations of Long and Fry (1945) and of Vogt (1944) showing that an injection of adrenaline causes secretion of A.C.T.H. and of adrenal steroids, the patient's records were examined to see whether the injections of adrenaline were followed by any significant increase in the outputs of cortins, of 17-ketosteroids, or in the U/C ratio. No such evidence could be found. The contrary effect, however, was well marked. Fig. 1 shows how the administration of adrenal cortical steroids (line F) caused the sensitivity to adrenaline to rise, though only temporarily. The significance of these facts is discussed below.

SENSITIVITY TO INSULIN.

In view of the results of Freeman and Elmadjian (1947), of Horvath and Friedman (1941), of Meduna *et al.* (1942), and of Freeman *et al.* (1943), a special interest attaches to the values to which the blood-glucose fell at 30 minutes after the intravenous injection of insulin. Recording this fall as a percentage of the resting value, Fraser and Smith found the normal fall to be always more than 50 per cent., and Meduna (1950) found the average fall to be 57 per cent. In this test our patient's blood-glucose fell, on five separate tests, by 28, 45, 32, 33, and 35 per cent. She was therefore undoubtedly somewhat resistant to insulin.

The resistance hardly varied. E.C.T. seemed to have no effect on it, either near the day of convulsion or over the whole of the investigation. Neither the outputs of cortins and of 17-ketosteroids nor the U/C ratio showed in their day-to-day variations any tendency to correlate with the insulin sensitivity.

These are the primary facts and their immediate consequences. It now remains to discuss their interrelations.

DISCUSSION.

The aim of these studies was to see whether they would provide information about E.C.T.'s mode of action. Some information has been obtained, but the studies have tended rather to raise new problems than to solve old ones.

The patient provides us first with the fact that E.C.T. invariably changed her state from one of catatonic stupor to one of apparent normality. To what somatic or cerebral processes can this change be attributed? In attempting to answer this question we should bear in mind certain facts.

First, E.C.T. undoubtedly has direct actions on the cerebral metabolism. Within a few seconds many of the energy-rich phosphatic radicles move from

phosphocreatine to glucose or glycogen (Dawson and Richter, 1949); and the oxygen-tension falls rapidly, even before the onset of the convulsion if induction has been slow (Davis *et al.*, 1944). Whether such changes were the effective factors in our patient is a question outside the scope of our investigation; but the possibility should be borne in mind.

More relevant to the investigation is the possibility that the treatment worked through the hypothalamus and adeno-hypophysis. It is known that the convulsing current, guided by the different electrical conductivities of the different parts, passes chiefly through the basal structures (Lorimer *et al.*, 1949). Direct stimulation of the hypothalamus is therefore to be expected. If this occurs, the excitation is likely to stimulate the adeno-hypophysis, conveyed either by the nerves known to pass to it from the hypothalamus (Vazquez-Lopez, 1949), or by hormones, still hypothetical, such as the granules described in the supraoptic and paraventricular nuclei by the Scharrers (1937), which would pass down the portal veins from the nuclei to the gland (Wislocki, 1938). It is not impossible, too, that the adeno-hypophysis is itself, in some way, directly sensitive to stress, for Cheng *et al.* (1949) showed that adeno-hypophyseal tissue still responds to stress of the animal (injection of histamine) by releasing A.C.T.H. even though the tissue has been transplanted to the spleen or the anterior chamber of the eye. That the adeno-hypophysis should be activated by E.C.T. is therefore by no means improbable; and the thesis is supported by the fact that the neurohypophysis is certainly activated: Altschule *et al.* (1948) have shown that E.C.T. is followed by haemoconcentration and the whole syndrome of neurohypophyseal activity.

Stress of any kind normally evokes a secretion of A.C.T.H. Of particular interest in relation to our patient is the demonstration by Recant *et al.* (1950) that among the evokers is adrenaline, for when this substance is injected into the normal person, the number of circulating eosinophiles, now known to be an excellent indicator of A.C.T.H. production, falls sharply. It would have been of great interest to have tested our patient in this way, to see whether adrenaline's inability to raise her blood-pressure was accompanied by an inability to evoke A.C.T.H. Unfortunately, the method of estimating A.C.T.H.-production by observing the circulating eosinophiles had not been published at the time and the possibility was unsuspected. There are other lines of evidence suggesting that in our patient some production of A.C.T.H. occurred after E.C.T. The U/C ratio was found to be raised, and the sugar-active cortins showed some evidence of increased excretion, both changes, so far as is known, accountable for only by a secretion of A.C.T.H. The amount secreted, however, can hardly be large. Moderate doses of the pure hormone (Thorn *et al.*, 1947; Mason *et al.*, 1948) readily increase the excretion of cortins by five times and that of 17-ketosteroids by three times. Our patient, however, showed only a small increase in cortins and none in 17-ketosteroids. The rise in U/C confirms this, for instead of the four times increase reported by Thorn *et al.* (1948) it rose by only 32 per cent. There seems, therefore, to be clear evidence that E.C.T. in this patient caused some secretion of A.C.T.H. though the amount was small.

Can this secretion account for the improvement in her mental state caused

by E.C.T.? The effect of A.C.T.H. on the mental state has been reported variously. Hench *et al.* (1949) and Spies and Stone (1950) reported that patients suffering from rheumatoid arthritis and treated by A.C.T.H. often showed marked elation and even euphoria; but it is difficult to make allowance for the effect of the sudden hope that their invalidism might end. Giving the hormone to normal subjects, Thorn *et al.* (1948) and Sayers *et al.* (1949) observed no particular emotional change, though the latter used amounts five to ten times as large as would be secreted after stress. Mason *et al.* (1948) even record that their normal subjects, given A.C.T.H., became pale, listless and apathetic, complaining of generalized malaise. Altschule *et al.* (1949) gave A.C.T.H. for some weeks to one depressed patient; it caused the usual fall in the circulating eosinophiles but no mental improvement; then the patient was given E.C.T.: though his eosinophiles responded less than before, his mental state improved markedly—an observation suggesting that E.C.T. has effects extra to those due to a possible forced secretion of A.C.T.H.

The second outstanding feature shown by our patient was her insensitivity to adrenaline. Such insensitivity has several times been observed in schizophrenics (e.g., Freeman and Carmichael, 1935; Freeman *et al.*, 1943). For a variety of reasons, Gellhorn (1942) considers an inexcitability of the sympathetic to be a fundamental feature in the pathogenesis of this condition. Certainly the insensitivity of the schizophrenic seems to be an important feature, for in the merely neurotic the sensitivity to adrenaline is usually increased (Thorley, 1942).

A discussion of this insensitivity must, however, proceed with caution, for such patients are often insensitive to many other agents. Freeman (1940), for instance, found them less sensitive than the normal to dinitrophenol, Freeman and Rodnick (1940) found them unresponsive to breathing hot water-saturated oxygen, and Cohen and Fierman (1938) found them less than normally sensitive to thyroxin. These insensitivities are perhaps not all independent, for it is known that hypo- and hyper-thyroidism, experimentally produced, cause the adrenaline sensitivity to become, respectively, decreased (Houssay, 1946) and increased (Schulze, 1922). Similarly Dynes and Tod (1940) found that while their schizophrenics were insensitive to adrenaline, the same patients, contrary to expectation, were not abnormally sensitive to its antagonists like acetylcholine and its derivative carbaminoylcholine chloride.

On the other hand, our patient was peculiar in that her insensitivity was almost total. A dose sufficient to cause acute distress in a normal subject caused in her, after the first few administrations, either no response or a negative one—a result explicable only by supposing that the vagal mechanisms were hyper-active. In this respect the patient exemplifies Gellhorn's thesis to the extreme. Since E.C.T. had so favourable an effect in restoring her mental state, we might expect some change to be produced in her abnormal insensitivity, especially as Funkenstein *et al.* (1948) had found that in psychotics generally E.C.T. tended to increase the sensitivity to adrenaline, and as Gellhorn (1942) had shown how important a part is played by the autonomic balance in the reaction to E.C.T. Inspection of the protocols shows

nothing of the kind : well or ill, having E.C.T. or not, her insensitivity remains. One cannot help remembering that so, too, did her basic illness—her basic tendency to develop these phasic attacks.

Can her insensitivity be linked with her mental condition ? There is no doubt that adrenaline can powerfully affect the brain's functioning. Although, as is well known, it has no direct effect on the cerebral vessels, it increases the activities shown in the electroencephalogram, its intracisternal injection causes a rapid rise of the blood sugar (Leimdorfer *et al.*, 1947), it lowers the threshold for audiogenic fits in the rat (Stainbrook, 1947), it markedly inhibits the intensity of convulsion in the cat (Gellhorn *et al.*, 1939), and it inhibits the sympathetic centres in the hypothalamus (Gellhorn, 1942). This last action on the hypothalamus may perhaps explain how it acts on the adeno-hypophysis, for such action is well established. Vogt (1944) showed that adrenaline caused an outpouring of cortical steroids from the adrenal vein ; she thought the substance acted directly on the gland, but Long and Fry (1945) showed that the adeno-hypophysis was involved, for though readily evoked in the intact animal, the reaction failed in the hypophysectomized, even though the adrenal cortex had been preserved from atrophy by regular injections of A.C.T.H. In man the action of adrenaline on the adeno-hypophysis is less readily demonstrated : Recant *et al.* (1950) were unable to detect any significant change in the U C ratio, in the excretion of 17-ketosteroids or of 11-oxy-steroids after a dose of 0.3 mgm., though they were able to show that some action had occurred, for the number of circulating eosinophiles fell sharply. The action seems to be reciprocal, for there is evidence that the sensitivity to adrenaline is sustained at least in part by the adeno-hypophyseal-adrenocortical system : thus the hyperglycaemic response to adrenaline is much diminished by both hypophysectomy (Safford *et al.*, 1946) and by adrenalectomy (Thomson, 1938). A further complication which cannot be ignored is the possibility that the patient's insensitivity is due to some abnormality in the mechanisms of inactivation, which, in this case, would have to be excessively active. Whether the necessary increase in activity is possible may be doubted. If the inactivation occurred, as was thought originally, through oxidation by amine oxidase, the sensitivity should be restored when inhibitors such as ephedrine or amphetamine were given ; but such was not the case. If the inactivation occurred through conjugation at one of the phenolic hydroxyl groups by the "sulphosynthase" system, as suggested by Richter (1940), this system, responsible for the conjugation of toxic phenols with sulphate, would have to be hyper-active, whereas such evidence as there is suggests that in schizophrenics the detoxicating systems are either normal or less active. The evidence therefore seems against any suggestion that the insensitivity was due to an abnormality in the mechanisms of inactivation.

Finally the response to insulin. Here too the schizophrenic has been found resistant by many workers : Horvath and Friedman, (1941), Meduna *et al.* (1942), Freeman *et al.* (1943), Braceland *et al.* (1945).

Can the fact throw any light on the mode of action of E.C.T.? It can be coupled with the report of Meduna (1950) on a case which was markedly resistant to insulin and which was given E.C.T. At first neither clinical condition nor

insulin resistance altered; but after the seventh shock the two returned to normality together. There seems too little evidence, however, to justify extensive argument.

The fact that our patient was resistant to both adrenaline and insulin argues against a simple pituitary origin of the abnormality, for the pituitary usually affects them oppositely. Thus the hypophysectomized animal's sensitivity is increased to insulin but decreased to adrenaline. Neither is the patient's condition compatible with a simple over- or under-activity of the adrenal cortex, for this again affects them contrarily, under-activity affecting them like hypophysectomy (Arnett *et al.*, 1942).

CONCLUSION.

It will be seen, therefore, that the abnormalities found in this patient do not conform to any yet recognized pattern. It may be worth while to notice exactly in what she was unusual. First there was the fact that though E.C.T.'s effect on her mental state was obvious, its effect on her insensitivity to adrenaline and to insulin was undetectable. The second peculiarity is that though E.C.T. induced an increased output of sugar-active cortins and showed its effect on the adrenal cortex by an increased U/C ratio, and though the giving of adrenal cortical steroids increased the sensitivity to adrenaline, yet the treatment itself had no effect on the sensitivity. The simplest explanation would be that the extract contained some substance not included in the steroids produced by the patient's own glands, their productive metabolism being in some way disordered. That such a disordered metabolism can occur is shown by the observation of Somerville *et al.* (1950), who found that rheumatoid patients, given progesterone and compared with the normal, excreted a much higher proportion as pregnanediol; but whether such abnormal steroid metabolisms can occur in the schizophrenic must be regarded as a question for the future.

SUMMARY.

Reported is a study of a patient with a cyclic psychosis, treated by convulsive therapy. The treatment repeatedly terminated the attack; and because the cycle was predictable she offered unusual opportunities for an investigation into the factors responsible for the effect of the therapy.

Over several months, daily estimations were made of a number of indicators of biochemical and endocrine function, particular attention being paid to the adeno-hypophyseal-adrenocortical system.

The most important facts found were that E.C.T. caused a secretion of sugar-active cortins, that the patient was insensitive to adrenaline and to insulin, and that the insensitivity to adrenaline was corrected temporarily by adrenal cortical extract.

The interrelations and significances of these facts, being complex, are discussed in the paper.

I would like to express my indebtedness to Dr. G. W. T. H. Fleming for the facilities provided, to Prof. F. L. Golla for advice and interest, to Mrs. M. Bassett for the special psychological and psychogalvanic tests, and to Miss J. McDowall for expert technical assistance.

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CLINICAL, BIOCHEMICAL AND PHYSIOLOGICAL STUDIES IN CASES OF RECURRENT SCHIZOPHRENIA.

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DURING the clinical observation of a female patient suffering from recurrent schizophrenic attacks, it was noticed that each psychotic episode was associated with the appearance of acne, and also that during remissions the patient showed an unusual craving for salt. These observations, together with the automatic disturbances characteristic of the onset of attacks, suggested that the adrenal cortex might play a part in the metabolic changes in this type of case, particularly the changes in nitrogen balance which have been demonstrated by Gjessing (1932, 1938). The work here reported was therefore primarily concerned with investigating the possible relationship between adrenal cortex activity and nitrogen metabolism in two patients of this type.

Case 1.

A female, aged 30, has suffered from recurrent attacks of a schizophrenic nature since the age of 15. She is the eldest child of a well-adjusted upper middle-class family. The father is markedly obsessional and tidy, and has kept full and tabulated notes of all his daughter's illnesses. The mother is small, quiet and sensible. They seem a well-balanced pair, perhaps a little over-protective towards the patient. There is one brother aged 23, who is apparently a self-reliant person, who goes his own way, but is nevertheless loving to his family. He has had no illness similar to the patient's. There is no family history of mental illness.

The patient's early life and development was uneventful, and there were no neurotic traits during childhood. She left school at the age of 17, having matriculated with five credits. Her school days were apparently happy, but she took little interest in games and did not make many friends, partly on account of changes in school and, in later years, because of her illness. She began to menstruate at the age of 12, and her periods have been regular and of normal duration ever since except for occasional intermenstrual bleeding. She was well instructed on sex matters by her parents, and does not seem to have had any abnormal interests or fears. She has had no serious physical illnesses. Before the onset of her mental illness, in 1935, she was a sincere, sensitive girl who blushed readily. She had a keen sense of humour, was intense in her friendships, and showed no over-concern about herself. She showed no unusual swings of mood and did not readily become depressed.

This patient has had a total of about twenty periods of mental illness, of which three have been more severe than the rest and have necessitated her admission to hospital. These occurred in 1935, 1942 and 1947. The first attack began quite suddenly in May, 1935, when the patient was 15. No environmental precipitating factors are known. The patient suddenly burst out crying when doing homework and in the ensuing days became increasingly excited over homework problems, had bouts of retching at her meals, became strange in manner, and was aurally hallucinated. She is said to have fainted, and thereafter to have partially recovered although the retching continued. She was still attending school, but on 23 September said she thought she was going to die and thought her father was going to kill her. She wept herself into a frenzy and screamed. On admission to hospital in October she was found to be alert, intelligent and co-operative. She showed no concern at leaving her parents, seemed happy, and showed no thought disorder. She was well orientated, had a good memory, superior intelligence, but doubtful insight. She showed a gradual improvement, regaining insight into her illness and was discharged after being in hospital two months. The whole attack lasted seven months. The diagnosis made was "Emotional upset of puberty, schizophrenic in form." She returned to school, and during the next six years had a total of about ten attacks, lasting from three or four days to a month, in which she felt tired and dreamy.

In February, 1938, she became a nurse. At this time she ate voraciously, gained 2 stone in weight and became very drowsy. She went off to sleep very readily, especially after eating sweets, of which she ate large quantities. Six months later while still nursing she had returned to her usual weight, but was still lazy and resented interference. In September of that year she had an attack lasting a week during which she was home in bed in a state of depression and semi-stupor. She was feverish, dreamt of bombs and of children being rescued from the wards. At the end of a week she returned to her nursing and remained in this work until June, 1940, when she was discharged as unsuitable, having had three further attacks.

About a month later she joined the Land Army and was in this work for over 6 years. At first she did extremely well, put on weight, and was very happy, but one week before Christmas, 1941, she went off her food, and was occasionally found alone crying. On Christmas Eve she was found tying up her Christmas presents in the dark in the harness room. On Christmas Day she was strange in manner, excited, quick in speech, and decked out in unusual finery. She was found crying with her arms around a horse's neck. When invited to a party in the evening she turned up in her working clothes, remained completely silent throughout the evening and later disappeared. She was found by the police the following morning in a wood near the farm in a dishevelled and dirty condition, having been out all night. She had a ring on her finger and said that she had been married and had spent a happy bridal night.

On admission to hospital in January, 1942, she appeared bright and alert, answered questions in a somewhat automatic way, but showed no evidence of thought disorder. She gave a description of her experiences as if they were recalled to her as a dream, and seemed to have no memory whatever for having been out all night. Her description of the "dream" included many ideas of reference. While in hospital she recovered much of her insight. She had two short periods in which she became dazed, tearful, and apparently depressed. She fabricated a long story of intrigue in her previous job which certainly could not have been true. Her behaviour in both these attacks was strongly suggestive of a schizophrenic state.

Following her discharge in March, 1942, she returned to the Land Army, where she had attacks at intervals of about a year consisting of a dazed condition gradually lifting and leaving a depression lasting two or three weeks. They tended to come on in the spring, midway between menstrual periods, and often seemed to be precipitated by excitement or the prospect of increased responsibility. It was noticed that as an attack came on she began to smile more with the left side of her mouth than the right. Between the attacks she had been regarded by her friends as being quite normal, but did not mix readily with other people and showed very little deep emotion.

In March, 1947, her third severe attack began. The onset was more gradual than usual, and the patient knew it was coming on. It began with flushing,

excitement over trifles, loss of appetite and talkativeness. She became depressed and moody, said her mind was in a tangle, lost all interest in her environment and was continually recalling previous attacks and reproaching herself for them. She was worse in the mornings and had a fixed stare which tended to disappear as the day went on. Within a fortnight she began to stutter, recited long extracts from the Bible, and from the writings of Leslie Weatherhead. Admitted to this hospital 4 weeks after the onset of the attack, she was found to be of average build and showed no abnormalities of hair or fat distribution. Neurological examination, X-rays of skull and cerebro-spinal fluid were normal.

There was a great deal of fluctuation in her mental state. Noticeable changes occurred at intervals of about 3 to 24 hours. At times she appeared to be completely occupied with hallucinatory experiences, striking strange but graceful attitudes, blinking her eyes and turning her head in various directions. She would stand in a listening attitude with wide-open eyes, occasionally breaking into song, or would appear to be fighting off something with a tortured facial expression, her eyes blinking, her fingers in her ears or over her eyes, and her whole body writhing. In this phase she was almost inaccessible, taking no notice of her environment, completely neglecting herself, refusing food, biting her lips and chewing her hair and the bed-clothes. She was several times incontinent of urine and once of faeces. Her pulse was rapid, her temperature rose to 99° F. or even 100° F., her hands and face were hot and sweating and she jumped at any loud noise. She exhibited all the characteristic motor phenomena of catatonia—automatic action, catalepsy, flexibilitas cerea and perseveration, and at times extreme negativism. Her speech consisted during this phase of whispered fragments only, expressed with a pleading, troubled look. Although the subject-matter was incoherent she did seem to be making some attempt to explain her state. She would endeavour to write down the content of her thoughts, but succeeded only in producing meaningless jumbles of phrases.

At other times she would keep herself tidy, and although occasionally making "listening" or "fighting off" movements, would do what she was told, conversed freely and ate well. She was brighter, smiled readily and wrote copious notes about her thoughts. Her speech was much freer and her sentences were usually completed. Comments on her environment were accurate, rational and complete, although not frequent. Talk related to her thought processes and fantasy life, however, was disjointed, fragmentary, and sentences were left incomplete, or if completed, were disconnected, e.g., "I want to get better—but the little bells stopped ringing." Thus it was only possible to obtain a fragmentary idea of the content of her hallucinatory experiences and of her attitude to them. It is doubtful whether, even in the grossly hallucinated state, any delusional systems formed. Certainly in the more lucid intervals the patient always showed complete insight for the hallucinations, referring to them as dreams and trying to prevent their coming on. Although the "dreams" were extremely numerous and varied there were two which kept appearing in various forms. In the first one, which was more in evidence during the first week or so, she went up a hill, met Christ, kissed him, and had a child—the second Christ. The second dream, which occurred later, was about a box which could only be entered by a very small hole and in which were imprisoned various people. These hallucinations persisted throughout the night unless strong sedation was given.

This attack lasted approximately 6 weeks, and was followed by a remission lasting 4 weeks in which she was superficially normal, but still slightly stiff and hesitant in her movements and preoccupied with her illness. She discussed her attacks readily and with complete insight. She remained in hospital for a period of 4 months, during which time two further attacks occurred, each lasting 3 weeks. On her discharge she was apparently normal except for a slight clumsiness of movement and hesitancy of speech. She obtained a position as an unskilled laboratory technician, which she has held since. Her work has been satisfactory, except for occasional periods of several days during which she is rather vague in manner, slow in her movements, feels inwardly excited and has difficulty in concentrating. She has had one further brief attack, less severe than those described, and characterized mainly by clumsiness, thought-blocking, excitement and self-reproach without hallucinations. During this attack she was admitted to hospital for a period of 5 weeks.

INVESTIGATIONS.

During the patient's first admission to this hospital (1947), when she had three attacks, her second admission (1948) when she had one attack, and also during the intervening period, when she had occasional abortive attacks, a number of physical and metabolic investigations were made.

GENERAL PHYSICAL CHANGES.

Autonomic changes.—At the beginning of an attack there was a rise in the pulse-rate, which also showed variability (80–140 per minute). The blood pressure showed similar changes which were evident in both systolic and diastolic values (130/80–190/110 mm. Hg). The pulse pressure showed an increase. There was marked flushing of the face, and sweating of face, feet and flexures. A rise in rectal temperature of the order of 1–2° F. occurred. All these changes appeared 24 to 48 hours *after* the first sign of mental change, and persisted until just before improvement began. During a remission the pulse-rate tended to be low (50–60) and the blood pressure slightly low (100/60–120/70), with lower pulse pressure.

Weight changes.—A fall in weight (3–7 lb.) began at, or just before, the onset of an attack, and continued until the peak of the attack was reached. Thereafter an equivalent rise in weight began and this continued for several weeks. These changes may have been due to defective food intake, but occurred during minor attacks in which the patient's appetite appeared to be unimpaired. She is also more prone to develop attacks when her weight is low, and tends to stay well when her weight is high.

Acne.—The appearance of acne on the face, shoulders and back regularly accompanied all but the mildest attacks. It was usually slight at the onset of an attack, but became increasingly severe as the attack subsided, reaching a maximum some weeks later, then gradually disappearing. During complete remission acne occasionally appeared in mild form, particularly during menstrual periods, but never as severely as during and after an attack.

Menstruation.—The normal menstrual rhythm and the characteristics of the menstrual flow did not appear to be consistently modified in any way by the attacks.

Biochemical Investigations.

Methods.—The following techniques were used in both cases: serum sodium, modification of McCance and Shipp's method (Harrison, 1947 (i)); serum potassium, Jacobs and Hoffman's method (Harrison, 1947 (ii)); serum chloride, Whitehorn's method (Harrison, 1947 (iii)); blood urea, Archer and Robb's method (Harrison, 1947 (iv)); blood sugar, Hagedorn and Jensen's method; serum cholesterol, modification of the method of Schoenheimer and Sperry (1934); urinary creatinine, modification of Folin's method (Hawk *et al.*, 1947); urinary 17-ketosteroids, modification of method of Patterson *et al.* (1942); urinary urea, hypobromite method (Harrison, 1947 (v)); urinary chlorides, Volhard-Harvey method (Hawk, 1938); urinary pregnanediol, Guterman and Schroeder (1948); haemoglobin, Haldane method.

For purposes of simplicity biochemical values will be described as "low" or "high," the terms being relative. This does not necessarily imply that the values described are abnormal, but that the changes are significant in terms of the tests used.

Nitrogen metabolism.—It was not possible, with the facilities available, to make complete studies of nitrogen balance. The blood urea was normal at the onset of an attack (35 mgm. per cent.), rose at the height of an attack (53 mgm.), and fell to low levels as the attack subsided (15–25 mgm.) (Fig. 1). The urinary nitrogen fell to low levels (1.3–2 gm. per 24 hours) at the onset of an attack and rose rapidly at the peak of the attack (27–28 gm.), gradually returning to normal levels (7–11 gm.) during a remission.

Salt and water metabolism.—A marked diminution of urinary output, not associated with deficient intake, occurred during the early stages of an attack and was most marked just before the height of the attack, when the daily output was as low as 500–800 c.c. At this point a sudden change occurred and a profound polyuria began, which reached its maximum (4,000–4,500 c.c.) as the attack subsided and lasted for about 2 weeks.

During the early stages of an attack the serum sodium was high (370–380 mgm. per cent.), the serum chlorides were normal (615–625 mgm.) and serum potassium was low (14.5–15.5 mgm.). The daily urinary output of chlorides (0.5–3.5 gm.) and sodium (2.0–2.5 gm.) was diminished. As the attack subsided there was a linear fall in serum sodium (to 330–340 mgm.) and serum chlorides (to 580–590 mgm.) and a linear rise in serum potassium (to 17.2–17.4 mgm.). The daily urinary output of chlorides (10–14 gm.) and sodium (5–6 gm.) showed a progressive rise.

Carbohydrate metabolism.—The fasting blood-sugar level remained fairly constant, but tended to be high during an attack, and to fall to low-normal levels during a remission. Glucose tolerance tests indicated normal tolerance immediately prior to and during an attack, but extremely high, delayed curves were obtained as the attack subsided. Between attacks a gradual transition occurred from decreased to increased tolerance. Insulin sensitivity increased up to the peak of an attack and decreased thereafter, a moderate degree of insulin resistance being present during remission (Fig. 2). The dosage of insulin (0.5 unit per pound body weight) is one used regularly in this Institute in connection with E.E.G. studies and has been standardized on a series of normal subjects.

Basal metabolism.—Marked changes in the B.M.R. did not occur, the values obtained ranging between 90 per cent. and 120 per cent. of normal. The lowest values were obtained during a remission, and in the early stages of an attack; the highest values were seen as an attack was subsiding.

Blood picture.—The total white cell count showed a fall before and during the early stages of an attack, reaching a minimum (6,000–7,000 per c.mm.) at the peak of the attack. Thereafter the total count rose, and during remissions, although there were marked fluctuations, it was generally high (12,000–30,000 per c.mm.). The polymorph/lymphocyte ratio remained constant. The haemoglobin fell progressively up to the peak of an attack and thereafter gradually rose. The E.S.R. remained constant (2–3 mm. in one hour).

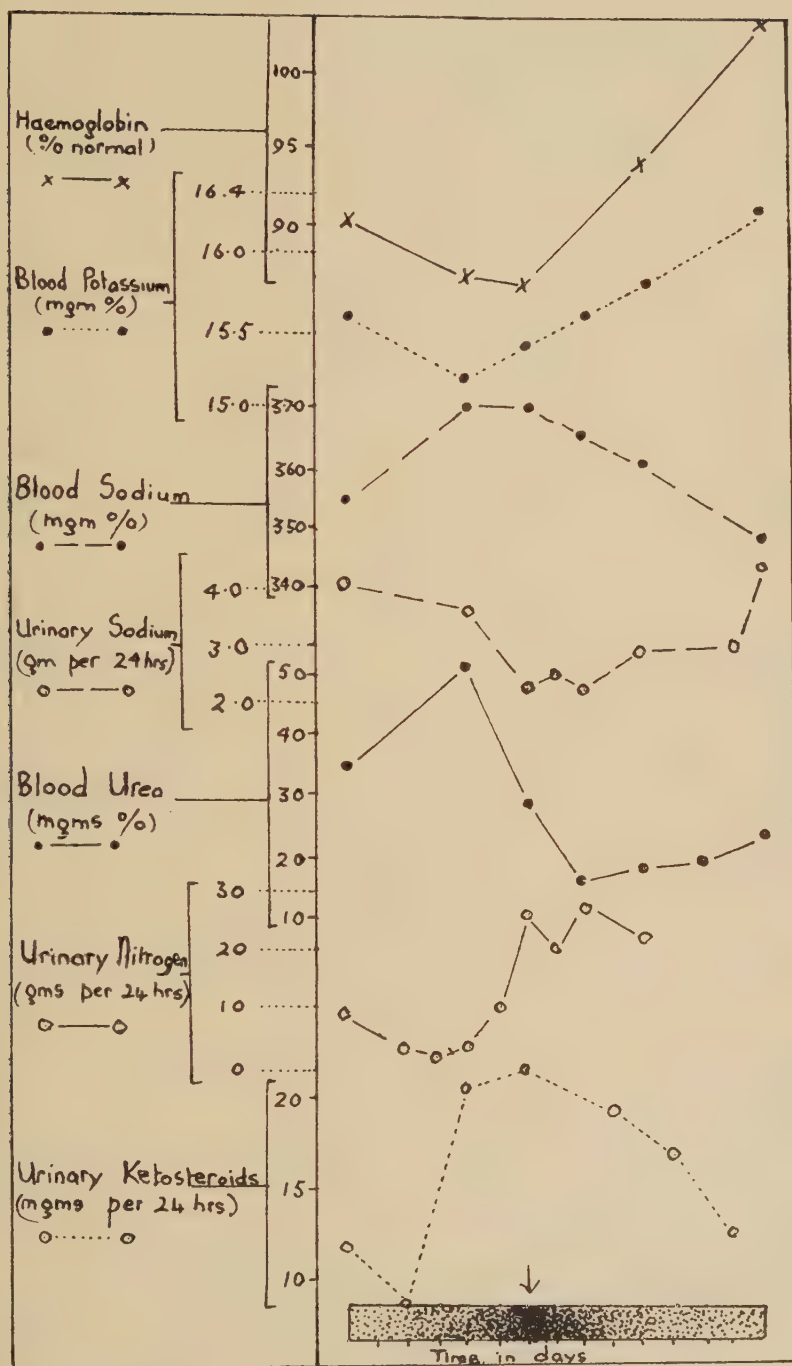


FIG. 1 (Case 1).—Biochemical changes occurring at peak of attack. Shaded area represents degree of mental abnormality. Arrow at peak of attack. Note reversal of trends at, or just before this point.

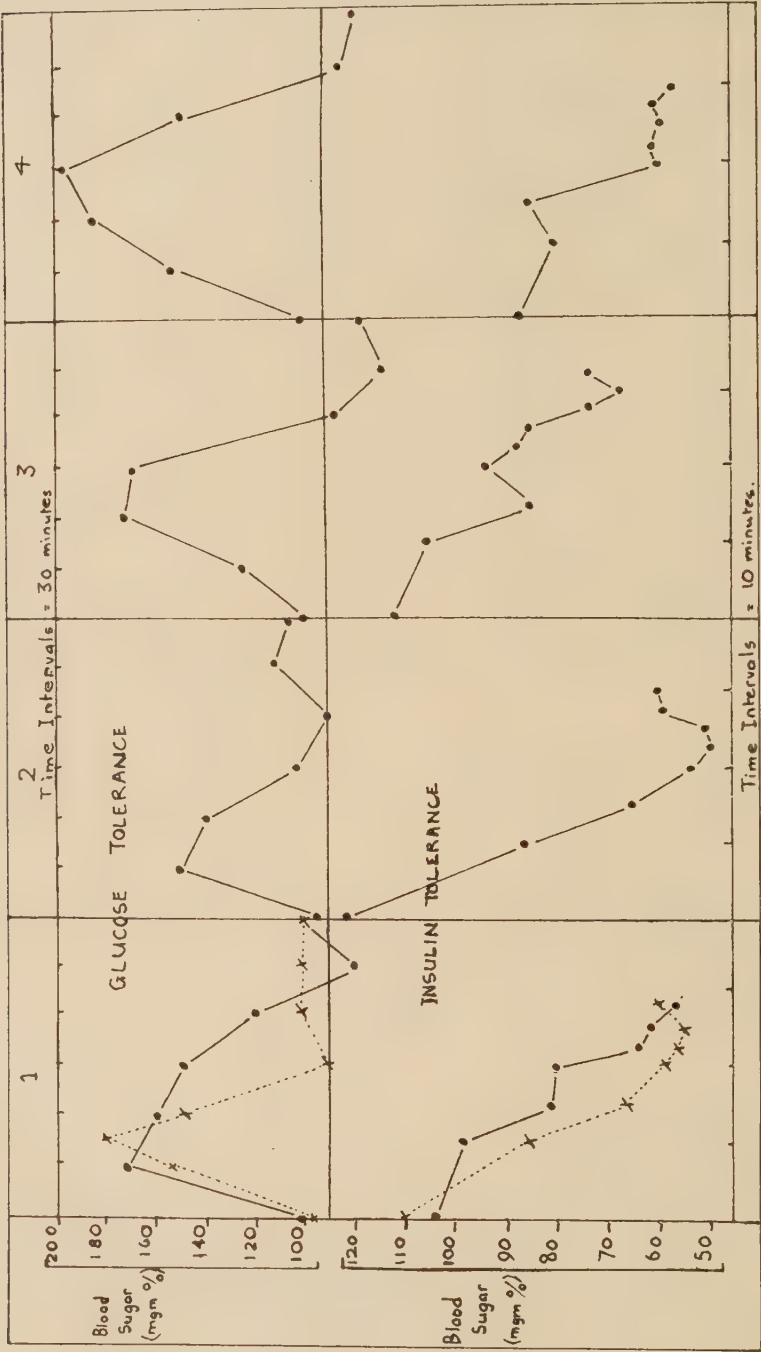


FIG. 2 (Case 1).—Glucose tolerance (50 gm. orally) and insulin tolerance (0.5 unit per pound body weight intravenously). (1) Entering an attack. (2) Near peak of attack. (3) Attack subsiding. (4) During remission. Normal curves are shown for comparison (+, . . . +).

Urinary excretion of 17-ketosteroids.—Fluctuations in the daily output of 17-ketosteroids were marked. In general, however, the excretion was high at the onset of an attack and subsided as the attack subsided.

It will be seen that the majority of the physical and metabolic functions studied show one trend before and during the early stages of an attack, a reversal at or just before the peak of an attack, and the opposite trend as the attack subsides (Fig. 1). The changes in these two stages are summarized in Table I.

TABLE I.—*Trends Observed Before the Peak of an Attack (Stage A) and After the Peak of an Attack (Stage B).*

	Stage A.	Stage B.
Pulse rate, blood pressure, temperature	Rise .	Return to normal
Body weight	Fall .	Rise
Acne	Mild .	Marked
Blood urea	Rise .	Fall
Urinary nitrogen	Fall .	Rise
,, volume	„ .	„
Serum sodium	Rise .	Fall
Urinary sodium	Fall .	Rise
Serum chlorides	Rise .	Fall
Urinary chlorides	Fall .	Rise
Serum potassium	„ .	„
Fasting blood sugar	Rise .	Fall
Glucose tolerance	High .	Low
Insulin sensitivity	„ .	„
B.M.R.	Low .	High
Total white cell count	„ .	„
Haemoglobin	Fall .	Rise
Urinary ketosteroids	Rise .	Fall

Electroencephalographic Changes.

This patient's E.E.G. was rarely within normal limits. Diffuse irregular low voltage slow activity at 4-7 cycles per second was almost constantly present. It was most marked in the left hemisphere, and was particularly evident in temporal and central leads. However, some characteristic changes in both the degree and type of abnormality occurred consistently in association with the attacks. The amount of irregular low voltage slow activity increased progressively before and during the early stages of an attack and was most marked at the height of the attack, when the slow activity became much more generalized and slower in frequency (as slow as 2 cycles per second). As the attack subsided the abnormality rapidly diminished and the most normal E.E.G. records were obtained at this time. During remissions the abnormality persisted in moderate degree, gradually increasing again before an attack.

At the times when this irregular diffuse abnormality was least marked (i.e., particularly during the early stages of a remission) another type of abnormality appeared consisting of bursts of 4-5 cycles per second activity of moderate voltage, the waves having a sharp appearance due to an associated increase in fast frequencies. This abnormality was also more evident on the left side and in the temporo-central areas.

Case 2.

A female, aged 30, has suffered from recurrent attacks of a schizophrenic nature since the age of 16. She comes from a comfortable middle-class home and is the eldest child of intelligent, but somewhat unstable parents. Her father, a successful professional man of asthenic build, is shy, diffident, dislikes making decisions and has had two neurotic illnesses. Her mother, a self-confident, determined business woman, is eagerly ambitious for her children, and excessively concerned over the patient's illness. A brother and sister, who are twins and three years younger than the patient, are both highly intelligent, artistic and popular. The brother is a painter and the sister an actress. There is no family history of psychotic illness.

The patient's early development was normal. Between the ages of 10 and 13 she had frequent severe epistaxes which did not occur with any periodicity. Although her schooling was interrupted by the onset of her illness, she was able to pass the School Certificate examination, enjoyed her schooling, and was good at games and acting. Menarche occurred at the age of 12 and was not associated with any physical or mental changes. Menstruation since has been regular and normal in amount, except in her most severe psychotic episodes. Her attitude to sexual matters has always been rather naïve and she has had no serious heterosexual attachments. As a child and adolescent she was bright, usually happy and never shy. She took part in social activities of many kinds and had wide literary and recreational interests.

The patient's illness began in the spring of 1934, at the age of 15. During the preceding few months she had been confirmed, had been kissed for the first time (and in consequence feared pregnancy), and had suffered three minor head injuries, two of which produced brief unconsciousness. Her illness began gradually with mild excitement, clumsiness, a tendency to laugh loudly and inappropriately and feelings of unworthiness. At this time she also complained of abdominal tenderness, palpitation of the heart and malaise, her skin was sallow and dry and her tongue was furred. The mental symptoms reached a peak in about 3 months, by which time her behaviour was strange and she was at times violent and uncontrollable; she felt that people were talking about her and spying on her. She talked of marrying a strange man, claimed that she was pregnant, and that the child would be Jesus Christ. She was aurally hallucinated. Over the succeeding 12 months a gradual improvement occurred, and by September, 1935, she was able to return to school for a period of 6 months. During this time, although she was able to pass her School Certificate examination, the remission was not complete. She remained slightly clumsy, apathetic and emotionally labile; she was less popular at school and ill at ease in male company.

In the spring of 1936 a second attack occurred which lasted 6 months and was again followed by partial remission. Since that time she has had recurrent schizophrenic episodes similar to that described above, which have tended to come on in the spring and have lasted for varying periods from several weeks to a year. In each attack a characteristic sequence of mental changes occurs which will be described later. The length of remissions has varied from a few weeks to two years, but at no time has she regained complete normality. During remissions she drives a car, goes shopping and is not considered eccentric, but is quiet, rather apathetic and lacking in judgment. She does not regain insight for her attacks. During her longest remission of two years (1939-41) which followed insulin coma treatment (40 comas) she worked successfully as secretary to the matron of a hospital, who reported that she was bright, cheerful and reliable.

The majority of her attacks necessitated admission to hospital and she has had a wide variety of physical treatments. These have included several courses of insulin comas, which, with the exception of the course mentioned above, have been without effect, electroconvulsant therapy and electronarcosis, both of which produced brief remissions lasting approximately 10 days, and thyroid (ext. sic. gr. 3 daily), which was without effect. In December, 1944, a prefrontal leucotomy was performed and this was also ineffective.

During the last 5 years the illness has assumed a definite periodicity, each attack lasting 6 weeks with remissions of 3 weeks. The periodicity was uninfluenced by leucotomy. A number of rhythmically occurring physical changes have been associated with different stages of the cycle. During a remission the patient eats ravenously, including excessive amounts of salt, drinks large quantities of fluid, tires readily and goes to bed early. When an attack is coming on her pulse is more rapid and there is a fine tremor of her hands. She sits up late, is restless at night, tends to hiccough, and her breathing becomes progressively more shallow with occasional deep gasps. During an attack she eats poorly, refuses meat in the early stages, loses weight, her hair becomes greasier, her complexion becomes pale and sallow, her lips are bloated and dry and respiration is almost invisible. Towards the end of an attack acne appears on her face and back, hiccoughing and gasping again occur and deeper respiration is re-established.

This patient, who also shows no abnormalities of build or hair distribution, has been under constant observation for a period of 18 months, during which time frequent clinical and biochemical observations have been made. The attacks have continued with the same periodicity, and with a characteristic sequence of mental changes. Each attack is heralded by a period of mild excitement lasting several days during which she is over-active, talkative and facetious, makes silly remarks and laughs excessively. Towards the end of this stage she becomes slightly aggressive, haughty and abrupt in manner and behaves as if aurally hallucinated. Gradually she becomes slower and more lethargic, neglects herself and giggles frequently. Her remarks become strange and symbolic, and rather bizarre, mildly grandiose delusions appear. She believes she is a royal princess, a musical composer or the bearer of a divine child. In the fully developed attack she is lethargic, off-hand and aloof in manner and shows marked thought disorder. Her replies are brief, superficial, vague and irrelevant. There are marked illogicalities and she leaves sentences unfinished. Her affect is shallow and inappropriate and there are ideas of reference and passivity feelings. The delusion that she is pregnant appears regularly, and before the attack subsides she claims to have had a child, but shows no interest in its nature or whereabouts. Towards the end of an attack there is a period of several days during which she is markedly irritable, paranoid, criticizes other patients and the staff, and tries to make "nasty" remarks, many of which are so disjointed as to be meaningless. The attack ceases quite suddenly over a period of hours and she becomes cheerful, pleasant in manner, smiles readily and appropriately and talks freely without disjointedness. She is careful of her appearance, shows normal interest in her environment, and is able to indulge in normal social activities. The superficial appearance is one of complete normality, but she remains slightly lethargic, lacks initiative, shows slight thought disorder (superficiality, deficient conceptualization and tendency to symbolization), and has only partial insight.

INVESTIGATIONS.

Although the investigations were continuous, they may be divided, for purposes of simplicity, into four periods, namely:

Period 1 (6 months): preliminary studies.

Period 2 (4 months): more complete investigations with the patient on a constant diet (for details of diet, times of examination, etc., see appendix).

Period 3 (3 weeks): effect of injections of adrenal cortex extract (patient on constant diet).

Period 4 (7 months): effect of thyroid administration (patient on constant diet).

Periods 1 and 2.—During these two periods, containing 8 attacks, the following changes were observed :

GENERAL PHYSICAL CHANGES.

Autonomic changes.—There were wide fluctuations in both the basal and non-basal pulse rate, but no consistent relationship was observed between these fluctuations and the changes in mental state. The basal blood pressure (systolic and diastolic), however, showed a consistent rise at the beginning of an attack, that is, during the period of excitement. It was not possible to say whether this rise in blood pressure, which lasted for 3–10 days, began just before or concomitantly with the first signs of excitement. Normal fluctuations of rectal temperature occurred in association with the menstrual cycles. There was a rise of temperature (1–2° F.) during the latter part of the intermenstrual phase beginning 7–17 days before the onset of a period, and a corresponding fall during menstruation. In one intermenstrual phase the rise in temperature was associated with a rise in pregnanediol excretion ; in other menstrual cycles tests for pregnanediol remained negative throughout.

No temperature changes associated with the fluctuations in mental state were consistently observed. Several days before an attack the skin of the extremities became blue and moist and “gooseflesh” was observed, particularly in the limbs. These changes in the skin persisted until after the peak of an attack, when they gradually disappeared. The pupils tended to become smaller before the onset of an attack and remained constricted until the peak of an attack, when a marked dilatation occurred which persisted until half-way through a remission.

Weight changes.—A consistent fall in weight (2–6 lb.) occurred during the 10 days preceding an attack and continued during the early stages of the attack. Several days before the end of an attack a corresponding rise in weight occurred, which reached its peak during a remission. These fluctuations in weight disappeared during Period 2 when the patient was receiving a constant diet.

Menstruation.—The menstrual rhythm continued normally throughout the investigation. The menstrual flow lasted 4–6 days and occurred every 24–28 days. It is of interest that the attacks occurred at almost exactly half the frequency of the menstrual periods, the onset of an attack occurring during, or just after, one period and recovery occurring during, or just after, the subsequent period.

Acne.—The occurrence of acne was much less marked in this case than in Case 1. When it occurred it was mild, and did not show any constant relationship to the cyclic changes in mental state. It tended to appear during the latter half of a menstrual cycle.

Biochemical Investigations.

In this case, owing to the patient's lack of co-operation, the completeness of many of the urinary specimens was in some doubt. The output of creatinine

varied widely (0.6–3.6 gm. per 24 hours), and although, in interpreting results, allowance has been made for this factor, all the urinary findings mentioned below must be regarded as doubtfully valid. No other investigations were affected in this way.

Nitrogen metabolism.—Before and during the first part of an attack the blood urea was low (18–28 mgm.). Near the peak of an attack a marked rise

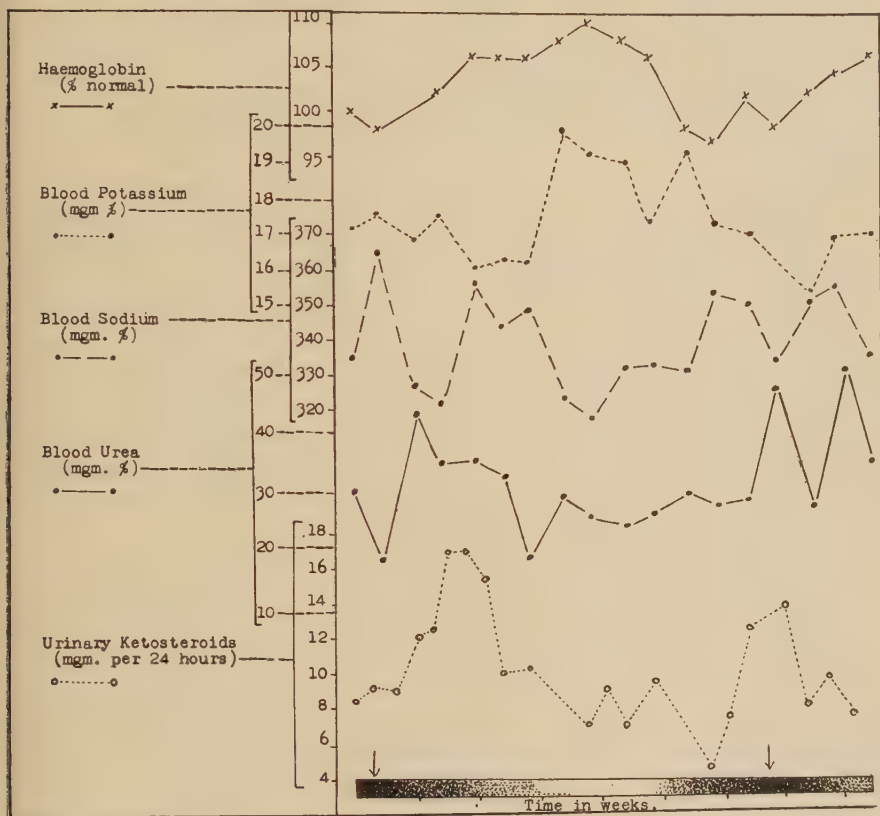


FIG. 3 (Case 2).—Biochemical changes occurring during two attacks and intervening remission. Shaded area represents degree of mental abnormality. Arrows indicate peaks of attacks.

occurred, the maximum (40–65 mgm.) being reached as the attack subsided (Fig. 3). These changes in blood urea continued during period 2, but towards the end of this period became less marked. A rise in blood urea was associated with a reduction in the urinary excretion of urea (12–15 gm. per 24 hours) and diminished clearance (as low as 30 per cent. of normal). As the blood urea fell there was a rise in the urinary urea (to 27–30 gm.).

Salt and water metabolism.—Although marked changes in urinary output of the degree observed in Case 1 did not occur, there was a gradual increase

in the difference, fluid intake less fluid output, during the early stages of an attack, and at the peak of an attack the difference was reduced. The level of blood haemoglobin fell before and during the early stages of an attack (to 94 per cent. of normal) and rose as the attack subsided (to 110 per cent. of normal). A rise in serum sodium (350–390 mgm.) and fall in serum potassium (15–16 mgm.) occurred during the early stages of an attack. After the peak of an attack a fall in serum sodium (310–320 mgm.) and a rise in serum potassium (19–20 mgm.) occurred. Changes in serum chlorides were not marked (range 580–640), but tended to parallel the serum sodium. Fluctuations in the urinary excretion of sodium and chlorides were considerable, in spite of the fact that the salt intake was kept constant. No more can be said than that the trends tended to be the opposite of those seen in the blood. All the above changes in electrolytes tended to become less marked towards the end of Period 2.

Carbohydrate metabolism.—No significant trends in the fasting blood-sugar level were observed (range 70–110 mgm.). It was not possible to do glucose tolerance tests because of the necessity for keeping the diet constant. Insulin tolerance tests, however, were performed weekly (0.1 unit per kilo body weight). During a remission and for the major part of an attack a marked degree of insulin resistance was present (Fig. 4). In 40 per cent. of the tests no significant fall in blood sugar occurred. In the remainder the fall only once exceeded 30 mgm. and the subsequent rise was rapid and prolonged. As the attack subsided, however, an almost normal degree of insulin sensitivity was present, the blood-sugar level falling by 40–60 mgm., but on only one occasion did it fall to less than half the fasting level within 25 minutes.

Basal metabolism.—The B.M.R. was consistently low (60 per cent. to 85 per cent. of normal) and did not vary significantly during attacks.

Blood picture.—Changes in the level of haemoglobin have been previously mentioned. There were wide fluctuations in the total white cell count (6,000–15,000 per c.mm.), and it was difficult to determine any consistent relationship between it and the other factors observed. In general, the count tended to be high when the blood urea was high (i.e., during the recrudescence of an attack) but this relationship was not consistent. During one of the periods when the total count was low, a “shift to the left” in the differential polymorph count was observed and there was a relative lymphopaenia and eosinopaenia. The E.S.R. tended to be slightly raised (4–12 mm. in one hour), fluctuated considerably and showed no significant cyclical changes, except perhaps for a slight inverse correlation with the white cell count.

Urinary excretion of 17-ketosteroids.—The daily excretion of 17-ketosteroids was low at the onset of an attack (4.0–6.0 mgm.) and rose as the attack progressed, reaching a maximum (12.0–17.0 mgm.) shortly after the peak of an attack.

The relationship of the main physical and biochemical changes to the peak of an attack is summarized in Table II. It will be seen, however, that the rise in blood urea and the rise in urinary 17-ketosteroids occur later in relation to the other changes than in Case 1 (Fig. 3). The significance of this will be discussed later.

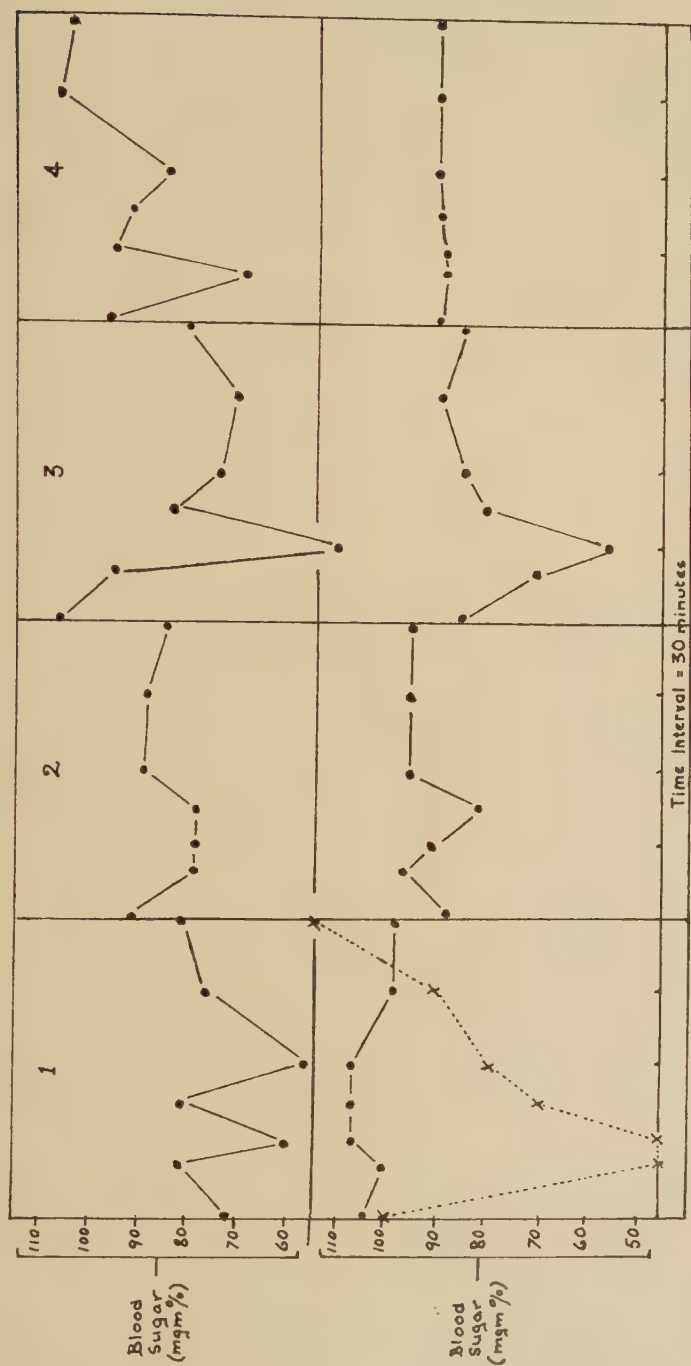


FIG. 4 (Case 2).—Insulin tolerance (0.1 unit per kilo body weight). Specimen curves. (1) Entering an attack. (2) Near peak of attack. (3) Attack subsiding. (4) During remission (the upper curve was obtained earlier in a remission than the lower curve). A normal curve is shown for comparison (+ . . . +).

TABLE II.—*Metabolic Changes Before the Peak of an Attack (Stage A) and After the Peak of an Attack (Stage B).*

	Stage A.	Stage B.
Cyanosis, "gooseflesh" and sweating .	Increasing .	Decreasing
Respiratory excursion	Diminishing .	Increasing
Body weight	Fall .	Rise
Blood urea	" .	"
Urinary urea	Rise .	Fall
" output	Fall .	Rise
Serum sodium	Rise .	Fall
Urinary sodium	Fall .	Rise
Serum chlorides	Rise .	Fall
Urinary chlorides	Fall .	Rise
Serum potassium	" .	"
Blood haemoglobin	" .	"
Insulin sensitivity	Low .	Normal
Urinary ketosteroids	Fall .	Rise

Electroencephalographic Changes.

The E.E.G. changes in this patient were similar to those observed in Case 1. Irregular low voltage slow activity was present in the great majority of records. In this case it was predominantly frontal and slightly more marked on the left. It was most marked during the early stages and at the height of an attack and diminished as clinical improvement began. As each attack subsided, and during the early stages of a remission, paroxysmal bursts of slow activity of higher voltage and an increase in fast activity were seen (Fig. 5). The two types of abnormality bore an inverse relationship as in Case 1.

Period 3.—Over a period of 5 days a total of 500 c.c. of "Eucortone" was given by intramuscular injection in doses of 20 c.c. five times daily. The investigations previously described were continued during this period and the subsequent two weeks.

At the time the injections were commenced the patient was in a partial remission, and a further attack was due to begin within a week or ten days. During the administration of the Eucortone she became slightly more withdrawn, negativistic and resentful, and there was evidence of increased aural hallucinations. On the second day of the injections two sudden outbursts of frenzied aggression occurred, in which she violently attacked the nurses and expressed bizarre paranoid delusions in an access of incoherent volubility, such as she had never previously shown. For a few days after the injections were stopped there was some slight improvement, but thereafter she again deteriorated and reached the peak of an attack 8 days after the last injection.

There was no significant change in pulse rate or blood pressure, and no changes in the skin of the kind previously described as associated with the attacks, but during the aggressive outbursts described above a marked pallor of the face was noted. A menstrual period occurred during the five days on which the injections were given. No fall in temperature occurred in associa-

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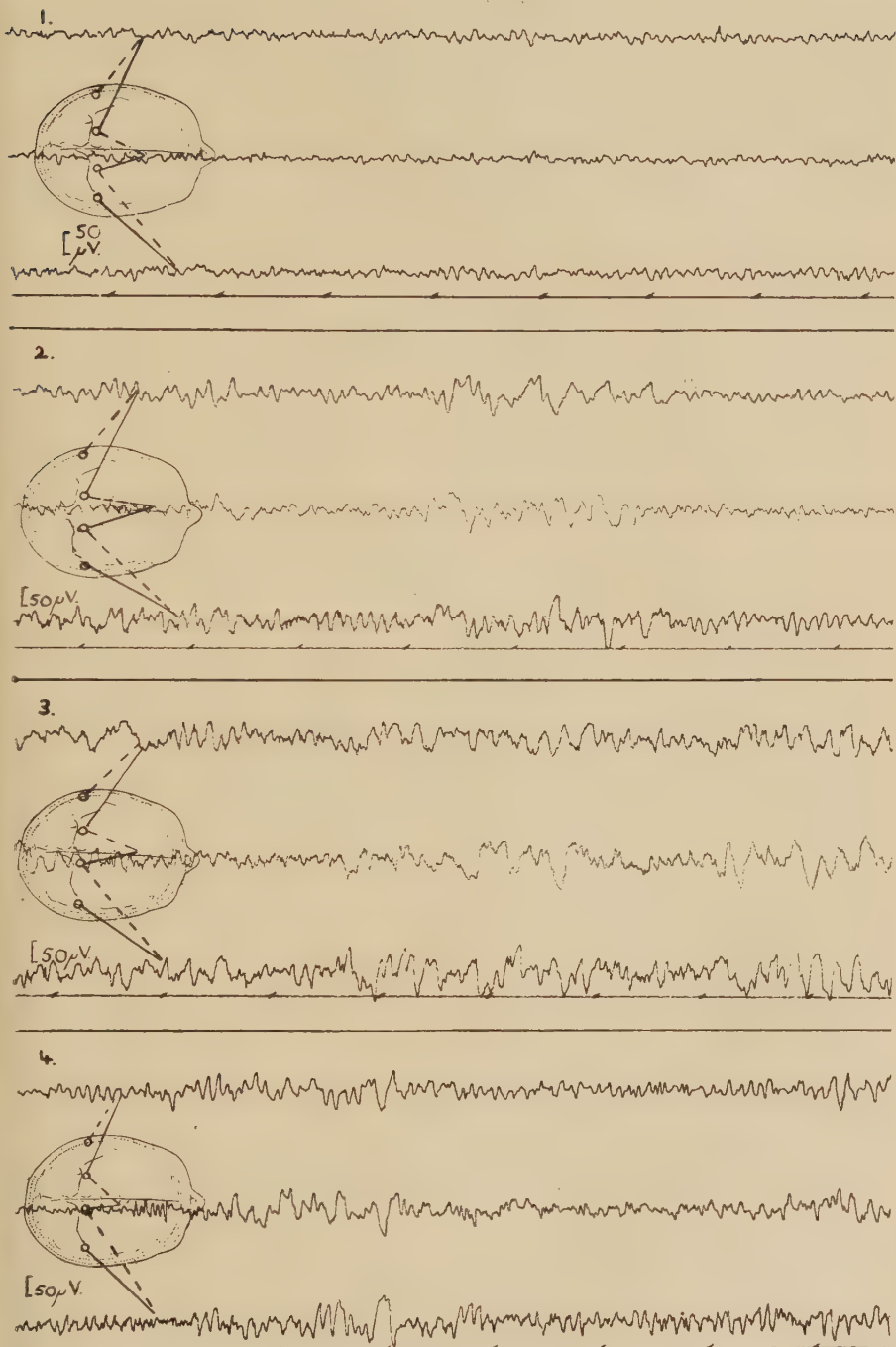


FIG. 5.—E.E.G. records from transverse temporo-central leads. (1) Early stages of attack. The E.E.G. is within normal limits, but shows minimal low voltage slow activity. (2) Early stages of remission. Appearance of paroxysmal slow activity of higher amplitude lateralized to the left; some increase in fast activity. (3) Eight days after commencement of thyroid administration. Marked increase of paroxysmal abnormality, now bilateral. (4) After 4 weeks of thyroid administration. Persistence of paroxysmal slow activity and further increase in fast activity.

tion with this period. There was a slight and probably non-significant fall in weight.

The blood urea showed a slight but not significant rise (2 mgm.), urinary urea a moderate fall (10 gm.), the serum sodium and chlorides a slight rise (10 mgm. and 20 mgm. respectively) and the serum potassium a slight fall (1 mgm.). There was a slight reduction in urinary output. None of these changes in themselves can be regarded as significant. The urinary excretion of sodium, chlorides, and 17-ketosteroids showed no significant change. Insulin resistance was marked. A significant increase in the sedimentation rate occurred (from 6-15 mm.), and on the third day there was a fall in haemoglobin (100 per cent. to 88 per cent.). There were no significant changes in total leucocyte count, lymphocyte count or eosinophil count.

The E.E.G. showed a slight increase in low voltage slow activity. The paroxysmal abnormality did not appear.

Period 4.—Thyroxin (racemic) was given daily by intramuscular injection in increasing doses (2, 4, 6, 8 and 10 mgm.), the injections being commenced 17 days after the last injection of Eucortone—that is, ten days after the peak of an attack. Thereafter thyroid extract sic. was administered orally in doses of 6 grains daily. Within eight days there was a marked improvement in the patient's mental state, and three days later she was in a complete remission. The pulse rate rose from 80 to 120, the blood pressure rose from 110/70 to 130/80 and there was a slight rise in rectal temperature. There was moderate sweating and a slight fall in weight. The blood urea rose (by 18 mgm.) and there was a marked rise in urinary urea (of 10-14 gm.). There were no significant changes in the serum or urinary values of sodium, potassium and chlorides. There was a gradual rise in 17-ketosteroids (6 mgm.) and increased insulin resistance. The B.M.R. rose to 108-115 per cent. of normal. The haemoglobin and sedimentation rate showed no significant change, but there was a fall in the leucocyte count (8,000-9,000 to 400-500) and a relative fall in the proportion of lymphocytes and eosinophils. At the time when the administration of thyroid was commenced, the E.E.G. showed moderate abnormalities of both types previously described. Within several days of the commencement of treatment, however, there was a marked increase in fast activity and in the paroxysmal fast and slow discharges, which were more frequent and of higher amplitude than any previously observed, this in spite of a blood sugar of 120 mgm. or higher (Fig. 5). These E.E.G. abnormalities persisted in gradually diminishing degree throughout the period of administration of thyroid.

Fifteen days after the last injection of thyroxin and while the patient was still receiving thyroid ext. sic. grains 6 daily there was a slight deterioration in her mental condition. During the preceding short remission the pulse rate, blood pressure and rectal temperature had gradually fallen and the blood and urinary urea had returned to pre-treatment levels. The "attack" lasted 9 days, ceased 3 days after the dosage of thyroid was raised to 8 gr. daily, and was associated with the characteristic physical and biochemical changes which occurred in the more severe attacks.

During the succeeding three months the patient had four such minor attacks, which tended to come on just before or during a menstrual period

(i.e., twice the frequency of her usual attacks). These minor attacks continued in spite of the fact that the dosage of thyroid was raised to 10 gr. daily and the B.M.R. was consistently above 120 per cent. normal. Each attack was associated with the characteristic physical and biochemical phenomena.

Thereafter, in spite of further increases in thyroid (gr. 12 and later gr. 14 daily), the patient again began to have more severe attacks with their original periodicity, lost a considerable amount of weight and showed moderate signs of thyrotoxicosis. The characteristic biochemical changes continued to occur in association with the attacks.

DISCUSSION.

The clinical similarity of the two cases presented is in many ways remarkable, even to the extent that both expressed delusions of pregnancy during attacks. A number of differences should, however, be pointed out. Although Case 1 showed the characteristic motor phenomena of catatonia during an attack the attacks did not occur with regular periodicity, whereas in Case 2, although there was a definite periodicity, the clinical symptoms in many respects resembled a hebephrenic state. Autonomic symptoms were also more marked in Case 1 than in Case 2.

From the point of view of nitrogen metabolism it is probable that Case 1 conforms with Gjessing's type A, the attacks beginning during a period of nitrogen retention, and that Case 2 conforms with Gjessing's type B, the attack beginning during a period of nitrogen excretion (Gjessing, 1932, 1938). Although the period of nitrogen retention in these two cases appears to be of shorter duration in relation to the attacks than in Gjessing's cases, strict comparison is not possible, since accurate studies of nitrogen balance have not been made. It is of interest, however, that in spite of the above difference in the time of occurrence of the nitrogen retention, the electrolyte changes bear the same time relationship to the peak of an attack in the two cases. In both there is a retention of fluid, haemodilution, retention of sodium and chlorides and excretion of potassium up to the peak of an attack, when the trends are reversed. These findings strongly suggest that there is increased activity of the electrolyte-controlling factor of the adrenal cortex. This occurs before and during the early stages of an attack, and begins to diminish at, or just before, the peak of an attack.

The appearance of acne, particularly during the later stages of an attack, was characteristic of both cases. This finding and the rise in 17-ketosteroid excretion suggest an increased output of androgenic substances, and it will be seen that there is a strong positive correlation between the 17-ketosteroid excretion and nitrogen retention, both occurring somewhat later in Case 2 than in Case 1.

In both cases the period of most normal insulin sensitivity coincides with the time when the blood urea is high, and in Case 1 the most normal glucose tolerance curves are seen at this time (cf. Figs. 1 and 2; cf. Figs. 3 and 4). Increased excretion of nitrogen, decreased glucose tolerance and increased insulin resistance, particularly during remissions, are in conformity with the suggestion that there is a predominance of the "sugar active" cortins at this

time. The leucocyte changes, although not conclusive, are also in conformity with this.

The following sequence of changes in adrenal cortex activity may, therefore, be postulated. Several days before the onset of an attack a progressively increasing activity of the electrolyte-controlling factor occurs, which reaches its maximum at, or just before, the peak of an attack. At about this time there is also an outpouring of androgenic substances. As the attack subsides, and as the activity of both these fractions diminishes, there is a progressive increase in the activity of the "sugar-active" fraction, and it is this fraction which is most active during a remission.

The times of occurrence of the two types of E.E.G. abnormality coincide closely with the periods of activity of these different fractions. The diffuse, low voltage slow rhythms appear when the electrolyte-controlling factor is most active, and the paroxysmal abnormality when the "sugar-active" cortins preponderate.

Although the majority of the biochemical changes can be explained on the basis of the above hypothesis, it must be admitted that there are changes the explanation of which is not clear. The fall in weight at the onset of an attack would not be expected as a result of the adreno-cortical changes, and must presumably be related to other factors. Also, although the retention of nitrogen associated with increased output of 17-ketosteroids suggests androgenic activity, a rise in blood urea would not be expected at this time, especially as there is increased activity of the electrolyte-controlling factor. It is perhaps important that the "sugar-active" cortins are least active at this point.

Of the effect of administration of adrenal cortex extract little can be said except that the changes observed, although characteristic, were remarkably slight as compared with those occurring in association with the attacks.

During the administration of thyroid there was little evidence of increased electrolyte-controlling factor or androgenic activity, but there is fairly strong evidence of increased production of "sugar-active" cortins. This is in conformity with the observation of Means (1949) in thyrotoxicosis. The marked E.E.G. changes of paroxysmal type which occurred during this period had occurred previously when there was evidence of a predominance of "sugar-active" cortins. The occurrence of slight mental changes in association with menstruation during this period is unexplained. It is possible that the decreased output of steroids at this time may have acted as a stimulus to the pituitary, causing secretion of corticotrophic hormone.

It is premature to suggest that changes in the relative predominance of the different cortical steroids bear a causative relationship to the periodic changes in mental state. However, it is important that the changes in electrolytes precede, and are invariably associated with the attacks. Also, there is some indirect evidence that the "sugar-active" cortins may be at least partially responsible for the remission in these cases. In the cases reported, remissions are invariably associated with the characteristic effects of "sugar-active" cortins and these effects appear as the attack is subsiding. The improvement produced by thyroid was associated with evidence of increased production of "sugar-active" cortins. E.C.T., of proven value in catatonia, and known to

produce temporary remission in Case 2, produces an increase in the urinary excretion of "sugar-active" cortins, whereas desoxycorticosterone does not produce mental improvement in cases which respond to E.C.T. (Ashby, 1949; Altschule and Tillotson, 1949). The E.E.G. changes in our patients suggest that "sugar-active" cortins may produce a state of cerebral excitation similar to that seen in epilepsy. It occurred when the patient's mental state improved either spontaneously or as a result of thyroid. Hill (1948) has previously reported E.E.G. abnormalities of an epileptic nature in this type of case, and also spontaneous convulsions, after which marked clinical improvement may occur. In Case 1 clinical improvement occurred on one occasion following a "faint," and on another occasion inhalation of amyl nitrite produced a convulsion which was followed by a marked improvement in the mental state. It is important, in view of the suggested association between epileptic disturbances in the E.E.G. and the activity of "sugar-active" cortins, that desoxycorticosterone has, if anything, an "anti-epileptic" effect (McQuarrie and others, 1942; Gellhorn and Ballin, 1946).

A dissociation between the secretions of the different adrenal cortical steroids has been observed after administration of adrenocorticotropin to man, the "sugar-active" fractions tending to show the greatest increase and also tending to appear earlier than the electrolyte-controlling fractions (Mason and others, 1948; Forsham and others, 1948). Ashby (1949) has observed a similar dissociation after E.C.T. It has also been shown that the effects of A.C.T.H. are dependent on the type of functional activity of the adrenal cortex (Lewis and Wilkins, 1949). Whether at some point in the cycle of events in the cases reported there is a discharge of A.C.T.H. it is not possible to say.

Further detailed investigation will be necessary to establish whether the changes observed are characteristic of this type of patient, to discover whether the postulated dissociation between adrenocortical steroids can be confirmed by additional studies, and to find what part is played by the pituitary in these changes.

SUMMARY.

Two cases of recurrent schizophrenia were investigated with a view to determining the relationship of adrenocortical activity to changes in nitrogen metabolism. Evidence is presented of a dissociation between different adrenocortical steroids, the various stages of an attack being associated with a relative preponderance of different steroid fractions, viz.:

1. Preceding and during the early stages of an attack, a preponderance of electrolyte-controlling factor.
2. At the height of an attack, a preponderance of androgenic substances.
3. During recovery and remissions, a preponderance of "sugar-active" cortins.

Two types of electroencephalographic abnormality are described, and these are related to different types of adrenocortical activity.

The significance of the findings is discussed.

ACKNOWLEDGMENTS.

We wish to express our gratitude to Dr. Denis Hill for permission to publish these cases, and for his constant help and encouragement during the investigations. We are also deeply indebted to Dr. Russell Fraser, University of London Postgraduate Medical School, Hammersmith Hospital, for arranging urinary sodium estimations and for his invaluable advice on endocrine problems. We also wish to express our thanks to Dr. J. Fairlie, of Allen & Hanburys, Ltd., for estimation of the constituents of "Allenburys Diet," to Mr. P. Chappell and Mr. H. V. Ridpath and their assistants for technical assistance in the biochemical estimations, and to Sister G. Harwood for her assiduous co-operation in the management of both patients.

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APPENDIX.

The daily diet administered to Case 2 was made up as follows:

Allenburys diet 15 oz. dried powder (2,000 calories, 62.0 gm. fat, 62.5 gm. protein, 277.5 gm. carbohydrate, chlorine 0.76 per cent., sodium 0.29 per cent., potassium 0.50 per cent.).

Halibol liq. 4 minims (vitamin A 4,000 i.u., vitamin D 1,300 i.u.).

"Roche" Vitamin B complex, Tabs. 1 t.d.s. (aneurin hydrochloride 15 mgm., riboflavin 6 mgm., nicotinamide 60 mgm., pyridoxine 6 mgm., calcium pantothenate 9 mgm.).

Folic acid 5 mgm.

Ascorbic acid 100 mgm.

Ferri et ammon. cit. gr. 10.

Soup powder 1 oz.

Egg powder 1 oz.

Matzos (unleavened bread), 2 biscuits.

Flavouring essences.

Orange cordial 100 c.c.

Distilled water as required.

} From same batch throughout.

Meals were made up from the above as follows :

8.0 a.m.	.	Allenburys diet, 2.5 oz. ; egg powder, 0.5 oz. ; Matzos, half biscuit.
10.0 a.m.	.	Allenburys diet, 1.5 oz.
12.30 p.m.	.	Allenburys diet, 4.5 oz. ; Matzos, half biscuit ; soup powder, 0.5 oz. ; cordial, 50 c.c.
4.0 p.m.	.	Allenburys diet, 2 oz. ; Matzos, half biscuit.
6.30 p.m.	.	Allenburys diet, 3.5 oz. ; soup powder, 0.5 oz. ; egg powder, 0.5 oz. ; Matzos, half biscuit ; cordial, 50 c.c.
8.30 p.m.	.	Allenburys diet, 1 oz.

The consistency and flavour of the Allenburys diet was varied by means of additions of distilled water and flavouring essences.

By venepuncture, blood was taken twice weekly for biochemical estimations at 11.0 a.m. On the day when insulin tolerance tests were performed the diet was withheld until after the test, the full daily amount being given during the remainder of the day. No biochemical estimations were done within 3 days of the insulin tolerance test.

RELATIONSHIP BETWEEN INSULIN COMA THRESHOLD OF SCHIZOPHRENIC PATIENTS AND THEIR RESTING E.E.Gs.

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THE E.E.Gs. of schizophrenic patients have been studied by a number of workers, notably Davis and Davis (1939¹). P. Davis (1939¹, 1940², 1942³) attempted a classification of schizophrenic records, defining the main types of pattern. Gibbs *et al.* (1938⁴), Jasper *et al.* (1939⁵), and, more recently, Hill (1946⁶), have noted the presence of epileptic activity in the E.E.Gs of catatonic schizophrenics.

Hill (1947⁷) has studied the changes in the E.E.Gs. of schizophrenics following the injection of insulin. More recently (1951⁸) he has postulated a central homeostatic mechanism acting in normal subjects during induced hypoglycaemia; and has shown that the homeostatic reactions of schizophrenic patients are different and would appear to be defective.

Hoagland, Rubin and Cameron (1937⁹, 1938¹⁰) and Himwich, Frostig *et al.* (1939¹¹) have studied the changes in the E.E.G. of patients undergoing insulin coma during and after treatment.

The present paper records an attempt to relate the characters of the resting E.E.Gs. of schizophrenic patients with their sensitivity to insulin, as demonstrated in the dose of insulin required to produce hypoglycaemic coma. As is well known the coma dose of insulin varies enormously in different patients. The E.E.G. of insulin "sensitive" patients have been found to differ, in several respects, from the records of insulin "resistant" schizophrenics.

MATERIAL AND METHOD.

The E.E.Gs. were studied in 54 adult schizophrenics, 37 male and 17 female, at St. Ebba's Hospital. Their records were, for the most part, made while they were waiting to have a course of comas. In a minority of cases the E.E.G. was recorded after the comas had been completed, but at least three months were allowed to elapse after the end of the treatment before the records were made. At the end of such a period the record can be expected to have returned to its pre-treatment form.

The coma dose of insulin was considered to be the number of units required to produce the first coma. The patients were treated under uniform conditions, dietary and otherwise, during treatment and standard criteria for diagnosing "coma" were employed. The patients were considered to be in

hypoglycaemic coma when they were completely unconscious, when they made no purposive response to painful stimuli, and when bilateral Babinski responses were obtained. In most cases the corneal reflexes were absent.

A six-channel Ediswan E.E.G. was used and with 43 patients full-length recordings were obtained, in the course of which the pens were actually writing for 15-18 minutes. With these records conventional electrode positions were used. In the case of 11 patients whose condition rendered prolonged recordings impossible, shorter records were made using 15 electrodes. In all but 2 cases overbreathing was attempted. Most of the patients had been fasting overnight, i.e., for 15-18 hours. The period of fasting was never less than 6 hours. The records were analysed in the usual visual manner, no automatic waveform analyser being available. For brevity the initials "C.D.I." have been used for the phrase "coma dose of insulin."

E.E.G. CHARACTERS STUDIED.

The following characters were considered against C.D.I. :

1. Alpha frequency of the resting record.
2. Presence or absence in the records of "theta activity" (activity at 4-7 c/s).
3. The presence of fast activity in the records.
4. The presence of paroxysmal activity in the records.
5. The "normality" or "abnormality" of the records.
6. The overbreathing responses.
7. The C.D.I. was also considered against the following factors :
 - (a) Sex differences.
 - (b) Age of patients.
 - (c) Duration of illness.
 - (d) Weight and body-type of patients.

RESULTS.

1. Relationship of Coma Dose of Insulin (C.D.I.) to Alpha Frequency of the Resting E.E.G.

TABLE I.

Alpha frequency (cycles per sec.).	Number of cases.	Average C.D.I. (in units).
Under 9 c/s	6	155
9-10 c/s	14	199
10-11 ,,	26	197
11-12 ,,	4	262
12 + c/s	3	60
No countable alpha	1	340

(N.B.—Results given here, as elsewhere, to nearest whole number.)

From these figures it appears that insulin sensitivity is not statistically related to alpha frequency. It is worth noting, however, that where the

alpha activity is slow (under 9 c/s) or fast (above 12 c/s) in our series of cases there is greater sensitivity to insulin. For frequencies within the 9-12 c/s range there appears to be no definite relationship between alpha frequency and insulin sensitivity.

2. *Theta Activity—the Presence or Absence in the Records of Activity at 4-7 c/s.*

The findings are set out in Table II. The "doubtful theta" group includes those records where only traces of slower rhythm were present. It will be noted that the grouping in Table II does not take into account the presence or absence of fast or paroxysmal activity, nor is the normality or abnormality of the records considered.

TABLE II.—*Theta Activity.*

Theta.	Number of cases.	Average C.D.I. (units).
Group (a) definitely present . . .	30	155
Group (b) doubtfully present . . .	5	222½
Group (c) definitely absent . . .	19	243

Comparing cases where theta activity is markedly prominent, we find that such records are associated with a greater degree of sensitivity than is shown by the whole theta group (Table III, below).

TABLE III.

	Number of cases.	Average C.D.I. (units).
Theta prominent	8	123
Theta present but not prominent	22	167
Total	30	155

These figures suggest that patients whose resting E.E.Gs. contain theta activity are likely to require smaller doses of insulin for their comas as compared with patients whose E.E.Gs. contain no theta rhythm. Taking groups (a) and (c) in Table II and comparing the mean coma levels by the *t*-students method for comparison of means, we find that the difference in the C.D.I.'s is statistically significant (p = less than .01). See also section 7 (b) below.

A most important point must now be considered; namely, the relation of age with the presence in the records of theta activity. It will be shown in section 7 (b) below that the theta minus group remains fairly constant in respect of insulin coma threshold; the theta plus patients under 21 years are much more insulin resistant than are the theta plus patients of 21 years and over. The theta plus group of patients over 21 years have an average coma dose of insulin of 131 units, as against the average dose for the theta minus group of patients over 21 of 241 units. The difference is 110 units—an even greater difference than when the records of under 21 years are included in the total, and is also a significant difference.

3. *The Presence of Fast Activity in the Records.*TABLE IV.—*Fast Activity.*

Fast activity.	Number of patients.	Average C.D.I. (units).
(a) Fast activity present and prominent	14 .	196
(b) Fast activity absent or only occasionally seen	40 .	191
(c) Fast activity and theta activity in same record	12 .	172
(d) Fast activity absent and theta activity present	18 .	144

The above table suggests that on the whole the presence of fast activity in a patient's E.E.G. is not significantly related to his sensitivity to insulin. In records containing slower rhythms, the presence of fast activity may be related to greater insulin resistance but not significantly so.

4. *Paroxysmal Activity.*

Seven of the records contained low voltage "spikes" of the type described by Jasper⁵ and Hill⁶. These records showed other evidences of paroxysmal dysrhythmia, and in every instance theta activity was also a feature.

TABLE V.—*Presence of Paroxysmal Activity in the Record.*

Type of record.	Number of patients.	Average C.D.I. (units).
Paroxysmal activity (containing theta)	7 .	151½
Whole "theta present" group	30 .	155

There is thus no reason to suppose that the presence of paroxysmal activity *per se*. has any relationship to the coma threshold.

5. *"Normality" or "Abnormality" of the Records.*

It is often very difficult to decide when the records of schizophrenics are abnormal. Their E.E.Gs. are frequently marred by artifacts, and in recent acute cases of the type that provides the majority of our subjects the records are frequently modified by the patients' state of tension.

Of our 54 cases, 6 records were considered to be doubtfully "normal" or doubtfully "abnormal." They will not be considered further. We considered that 28 records were undeniably normal and that 20 records were abnormal.

The types of abnormality encountered were (i) "paroxysmal" records and (ii) "non-specific dysrhythmic" E.E.Gs.; i.e., records containing a mixture of fast and slow activity; (iii) records containing an excess of theta rhythms with little or no fast activity.

TABLE VI.—*Relation between Normality and Abnormality of the Record and Insulin Coma Dosage.*

Type of record.	Number of patients.	Average C.D.I. (units).
(a) Definitely normal	28	225
(b) Definitely abnormal	20	153½
(i) Fast-slow dysrhythmic	5	170
(ii) Slow rhythms with little fast	8	145
(iii) Paroxysmal or epileptic activity	7	151½

The difference between the "normal" and "abnormal" groups is considerable as regards sensitivity to insulin. Comparing the mean insulin levels of patients in the two groups we find the difference in coma doses of insulin to be significant (p = less than 0.01).

Thus there is not much difference between the types of abnormality encountered in relation to their insulin sensitivity.

6. *Effect of Overbreathing.*

TABLE VII.—*Overbreathing Responses.*

Response to overbreathing.	Number of patients.	Average C.D.I. (units).
Increased instability	17	153
No appreciable change	35	212

It was impossible to obtain the co-operation of two patients in overbreathing.

The E.E.Gs. of insulin resistant patients tend to be more stable on overbreathing than do those of more insulin sensitive patients.

7. *Factors which might Affect the Coma Threshold.*

(a) *Sex differences.*—The average coma dose of insulin of 37 male patients was 195 units, and of 17 female patients was 186 units. No significant differences were observed between the sexes whenever numbers permitted a comparison.

(b) *Age.*—The relation between age and coma dose may be seen from the following table :

TABLE VIII.

Age.	Number of patients.	Average C.D.I. (units).
18-20 years	11	254
21-25 „	21	190
26-30 „	10	187
31-39 „	8	171
40 + „	4	90

At a first glance there appears to be some relationship between age and coma dose. Table IX, however, shows the distribution of theta plus and

theta minus records in the respective age-groups. Doubtful cases have been omitted.

TABLE IX.—*Relation between Age and Presence of Theta in the Records (doubtful cases omitted).*

Age group.	Theta activity, plus or minus.	Number of patients.	Average C.D.I. (units).
18-21 incl.	—	2	260
	+	8	244
21-25 „	—	9	237½
	+	10	125
26-30 „	—	5	228
	+	5	146
31-39 „	—	3	247
	+	4	130
40	—	0	0
	+	3	73

These figures show that on the whole there is little variation with age in the coma dose requirements for patients whose records contain no theta activity. The 3 patients over 40 years had all grossly abnormal E.E.Gs. and were remarkably sensitive to insulin.

The theta plus records of the juvenile group (under 21) showed much greater insulin resistance than did those of the group 21-40 years. Omitting the 40 plus age-group we find that, as previously mentioned, of the patients aged 21-40 years, those whose E.E.Gs. contained theta activity had an average coma dose of 131 units, while those without theta activity had an average C.D.I. of 241 units.

(c) *Duration of illness.*—We have arbitrarily taken 18 months from the beginning of illness as the dividing-line between “recent” and “long-standing” cases. To avoid misleading results, we have felt it preferable to confine our attention to the 39 patients in the 21-40 years age-group. We have been able to determine with reasonable accuracy the time of onset of 29 of these patients.

TABLE X.—*Duration of Illness 21-40 Group.*

Duration of illness.	Average age.	Number of patients.	Average C.D.I. (units).
“Recent” cases	27 yrs. 8 months	18	198
“Long-standing” cases	27 „ 9 „	11	150

(d) *Weight and body type.*—Assuming that theta activity has the most striking relationship to insulin sensitivity, we compared the weights of the “theta present” group of patients with the weights of the “theta absent” group.

Male patients: Average weight of theta + group, 9 st. 13 lb.

	„	„	theta —	„	10 „	1 „
Female	„	„	theta +	„	9 „	2 „
	„	„	theta —	„	9 „	3 „

Thus the weight *per se* is not related to presence or absence of theta activity in the records.

TABLE XI.—*Body Type: Relation between Body Type and Sensitivity to Insulin.*

Type.	Number of patients.	Theta present or absent.	Average C.D.I. (units).
Asthenic (male)	8	Theta +6 rcds. -2 „	162½
Pyknic and near pyknic (male)	7	Theta +2 rcds. -5 „	246

It would appear probable that insulin is related to body type as opposed to body weight. It is interesting to note that theta activity was related closely to asthenic build in these cases, but the numbers appear too small to provide anything other than an interesting observation.

We were unable to provide similar comparison between asthenic and pyknic female patients as the numbers involved would have been even smaller.

SUMMARY AND DISCUSSION.

The most significant results from this study were: (1) that taking the group of patients as a whole, those whose E.E.Gs. contained theta activity had comas on smaller doses of insulin than did those whose E.E.Gs. did not contain theta activity; (2) similarly, that patients with abnormal E.E.G. were more insulin sensitive than those with normal records, though the type of abnormality was of much less importance; (3) patients whose E.E.Gs. remained stable on overbreathing were more insulin resistant than were patients whose E.E.Gs. were unstable.

It is interesting to note that sex and weight were unimportant considerations, though the asthenic body-type, at least in male patients, appeared to be related to the presence of theta activity and to greater insulin sensitivity. This is a point which needs further study.

In patients over 21 years, age appeared to be of comparatively little significance in relation to insulin sensitivity, but in the young adult group (under 21) there was less sensitivity to insulin whether theta was or was not present. In fact, the difference between the theta plus and theta minus categories under 21 years was not significant. It is possible that some of the theta plus cases in this group come under the heading of what might be termed "normal immaturity," and, in fact, that these cases tend to behave more like mature adult records in relation to insulin sensitivity, i.e., show a comparatively high degree of resistance.

It is in patients over 21 years that the presence of theta activity in the E.E.G. has significance for insulin sensitivity. Such theta activity could represent immaturity; or some constitutional peculiarity (e.g., where it is combined with paroxysmal activity); or it might result from an acquired disorder of the brain. Perhaps in different E.E.Gs. theta has a different

significance. That theta activity occurs in a large proportion of the records of schizophrenics is not necessarily true of the older or more chronic patients, although in the patients studied there appeared to be little falling off with age proportionately in the incidence of cases showing theta activity.

Whatever the cause of the theta activity in adult schizophrenics, it suggests a disturbance in the integration of function between the cortex and basal structures. This disturbance may be due to a failure of development of normal cortico-basal interaction with resulting incomplete cortical dominance; or it may be due to acquired impairment of such interaction; or it may be due to abnormal functioning, e.g., the "tendency to convulse."

Davis (1943¹²) and later Hill (1947⁷) induced hypoglycaemia in a number of subjects and found that, where slow rhythms were present in the resting records, the E.E.Gs. during hypoglycaemia showed marked slowing at relatively high blood-sugar levels, i.e., that cerebral function, as shown by the E.E.G., was more vulnerable to changes in environment than was the case when no slow rhythms were present in the resting records. It is interesting to note that Hill *et al.* (1951⁸) has shown that homeostatic reactions to hypoglycaemia in schizophrenics are also defective and differ from those of normal subjects; their reactions to stress are imperfect, and it would appear that these reactions are also more vulnerable. It may be that the presence of theta activity in the more insulin sensitive group of our patients' E.E.Gs. is related to markedly defective homeostatic mechanisms which would render those subjects less able to resist the effects of insulin.

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PELLAGRA AND THE NUTRITIONAL NEUROPATHIES : A NEUROPATHOLOGICAL REVIEW.

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INTRODUCTION.

IT is now well recognized that many of the syndromes previously described as pellagra, such as nutritional retrobulbar neuropathy, the ataxic, and burning feet syndromes, may occur as isolated manifestations of nutritional deficiency. The term "pellagra," as it is often used, is no more than a generic title embracing a wide variety of nutritional disorders. The clinical status of the individual deficiency syndromes has been elucidated of late years in America (Spies *et al.*, 1939; Harris, 1941), and with particular regard to the neurological disorders, in groups of prisoners of war in the Far East (Denny Brown, 1947) and Middle East (Spillane, 1947). The majority of the pathological studies of pellagra were completed in the era before advancing biochemical knowledge provided the impetus to further these clinical studies, and this is reflected in the great diversity of neuropathological changes described as "pellagrous." The extensive literature contains many excellent studies of cases dying from malnutrition, and it now seems possible to attempt a correlation between the pathological findings and the more recently described individual syndromes. A review, therefore, of the neuropathological changes encountered in "pellagra" might be not untimely.

PERSONAL OBSERVATIONS.

The material consists of 14 fatal cases of nutritional disorder, diagnosed clinically as "pellagra." For the sake of brevity, the clinical and pathological findings are summarized in Table I.

From this table it may be observed that ten of these fourteen patients had been inmates of mental hospitals for periods exceeding one year. Their original diagnoses ranged from imbecility to schizophrenia, but during the course of their illnesses the diagnosis of a superimposed pellagra had been considered in eight, and treatment had been commenced with nicotinic acid, nicotinamide, and one or other of the vitamin mixtures. The one patient who had recovered with such measures had been originally diagnosed as an acute confusional insanity, and of all the cases presented the nearest approximation to a classical "pellagrous psychosis." The difficulties of diagnosis in a mental hospital population need not be stressed, but from a review of the case-histories it is clear that there are three criteria of great diagnostic

importance, (1) loss of weight, (2) diarrhoea and (3) dermatitis. This triad was common to all fourteen patients, and was of diagnostic importance in the above order. Loss of weight for no apparent cause, in the absence of both diarrhoea and dermatitis, should arouse suspicion of a deficiency state in a patient confined to a mental hospital. Both the diarrhoea and the dermatitis may appear at a later stage of the disorder and may be merely transient. Whether the loss of weight is causal or is an inherent part of the syndrome is, for practical purposes, unimportant. The approximate time relations of this diagnostic triad are shown in Table II.

In several cases the diarrhoea was treated with either sulfaguanidine, or with sulfasuxidine; in two patients this resulted in an exacerbation of both the dermatitis and the mental changes. One of these cases (Case 3) has been the subject of a previous communication (Hardwick, 1946). The diarrhoea, moreover, did not respond to this therapy.

The dermatitis characteristically was of the exposed parts, face, forearms and legs. In six of the fourteen patients exposure to the sun had precipitated the dermatitis, and in three of these patients there had been a recurrence of the skin condition on re-exposure to sunlight. A glossitis was observed in only six patients.

Signs indicative of a spinal cord lesion were observed in only three patients—in one, wasting of the small muscles of the hands was associated with a spastic paraplegia; in the second patient there was a dysarthria, gross generalized muscle wasting, and a spastic paraplegia; whilst in the third a spastic paraplegia was present. Epileptic attacks—occurring in series—were a feature of three cases, but their significance is difficult to assess in relation to the nutritional disturbance.

The histological changes in these cases were remarkably uniform. They are listed in Table I. It can be seen that the most constant finding was a retrograde cell change in certain groups of nerve cells. The term retrograde degeneration was originally introduced to describe the type of cell change associated with axonal damage. It may, however, occur in disorders where no axonal injury is apparent, in this case most probably indicating a disturbance of intracellular metabolism—in particular, of nucleo-protein metabolism. Recent studies (Bodian, 1947) have shown that during chromatolysis changes occur in the nucleic acid and creatine phosphate metabolism of the cytoplasm, and that intracellular enzymatic activity also is affected. Histologically, the Nissl bodies disappear from the centre of the nerve cell, a layer of chromatin substance remaining peripherally, and the nucleus becomes eccentrically displaced. These two criteria distinguish the retrograde cell change from simple "chromatolysis," where some general dissolution of Nissl bodies occurs, without any shift in nuclear position. In contrast to the retrograde cell change, the significance of chromatolysis is difficult to assess in pathological material.

In the material reported here a retrograde cell change was observed constantly in the giant cells of the pre-central cortex; in eleven cases the changes were severe, as manifested by almost complete absence of Nissl bodies, and nuclear eccentricity (Fig. 1). In two the change was less marked, and in the recovered patient no cellular abnormality was present, either in the Betz

TABLE I.

Case.	Length of stay in hospital and diagnosis.	Somatic manifestations.	Neurological manifestations.	Treatment.	Histological findings.
1. H. C—, male, aged 50	18 years. Epilepsy. Imbecility. Myocardial degeneration	Erythema of face. Loss of weight—3 stone in the last 3 years of his life. Diarrhoea	Bilateral wrist drop. Marked wasting of arms, forearms and small muscles of hands. Knee- and ankle-jerks absent	—	<i>Etat vermolu</i> ventral aspects right frontal and temporal lobes. Severe retrograde cell change in Betz cells, and in the nerve cells of the pontine, dorsal vagal, gracile, cuneate, ambiguous and descending trigeminal nuclei. Less severe retrograde cell change in nerve cells of vestibular nucleus.
2. R. H—, female, aged 18	6 weeks. Pellagra	Diarrhoea, loss of weight, difficulty in walking and tenderness of feet of 1 year's duration. Glossitis. Dermatitis of vulvae, anus, cheilosis. Dermatitis face	Wasting of small muscles of hands and feet. Spastic paraplegia	—	Severe retrograde cell change in Betz cells and in the nerve cells of the pontine, gracile, cuneate, dorsal vagal and vestibular nuclei. Nerve cells of oculo-motor nuclei less severely affected. In the spinal cord the anterior horn cells showed a severe retrograde degeneration, with neurofibrillary dissolution. Myelin stains revealed a lateral column degeneration, and with fat stains droplets of free fat could be seen in the lateral columns. Hyaline change in arterioles of cerebral cortex.
3. J. M. J—, female, aged 58	3 years. Manic-depressive psychosis. ? Pellagra	Loss of 56 lb. in weight over 2 years. Dermatitis of chin, upper chest and face. Glossitis, cheilosis, angular stomatitis, diarrhoea	None recorded	Nicotinamide riboflavine, yeast	Severe retrograde cell change in Betz cells (Fig. 1), in the nerve cells of the pontine nuclei (Fig. 2), and of the dorsal vagal, cuneate, gracile and trigeminal nuclei. Moderate retrograde cell change in neurones of nucleus ambiguus.
4. E. K—, female, aged 59	16 years. Epilepsy and Dementia. Pellagra	Loss of weight. Diarrhoea, and dermatitis of legs, face, neck and hands on exposure to the sun. Onset of stupor following a course of sulfasuxidine	Bilateral wrist drop, absent knee- and ankle-jerks. Plantar responses extensor	Nicotinamide and vitamin B ₁	Severe retrograde cell change in Betz cells; moderate retrograde cell change in neurones of pontine, dorsal vagal, gracile and cuneate nuclei. Hyaline change in arterioles throughout the brain.

Case.	Length of stay in hospital and diagnosis.	Somatic manifestations.	Neurological manifestations.	Treatment.	Histological findings.
5. B. P—, female, aged 49	9 months. Depressive reaction. Pellagra	Loss of weight. Diarrhoea. Oedema of feet, shins and vulvae. Dermatitis of face, and dorsal surfaces of hands. Glossitis	None recorded	Nicotinamide, vitamin B ₁ , riboflavin, vitamin C	Moderate retrograde cell change in Betz cells and in the nerve cells of the pontine nuclei. In the neurones of the dorsal vagal, cuneate and gracile nuclei an early retrograde change was present.
6. N. W—, female, aged 41	12 years. Dementia praecox. Hypostatic pneumonia	Loss of weight. Diarrhoea, dermatitis of hands, upper and lower limbs, and chest	"	—	Severe retrograde cell change in Betz cells, and nerve cells of the pontine nuclei.
7. J. H—, female, aged 50	2 years. Involutional melancholia. Pellagra	Dermatitis of face and heel. Diarrhoea	"	—	Moderate degree of retrograde cell change in Betz cells, and in nerve cells of the pontine, dorsal vagal, gracile and cuneate nuclei. Spinal cord: normal. Sciatic nerves: some increase in fibrous tissue.
8. V. C. T—, female, aged 24	7 years. Schizophrenia	Dermatitis of trunk and limbs, worse on exposure to sunlight. Loss of weight. Diarrhoea, glossitis	" Epileptic attacks "	—	Severe retrograde cell change in Betz cells, and in nerve cells of pontine and oculomotor nuclei. Moderate degree of retrograde cell change in neurones of gracile and cuneate nuclei.
9. A. H—, male, aged 49	15 years. Schizophrenia	Loss of weight. Dermatitis face and hands on exposure to sun. Diarrhoea	None recorded	—	Severe retrograde cell change of Betz cells and nerve cells of gracile, cuneate, trigeminal and ambiguous nuclei. Spinal cord: severe retrograde cell change in anterior horn cells.
10. D. M—, female, aged 44	25 years. Imbecility. Pellagra	Loss of weight. Diarrhoea. Ulceration of vulva and anus, dermatitis of hands and forearms. Glossitis, cheilosis	"	Polyvitamin mixture	Severe retrograde cell change in Betz cells and in nerve cells of the pontine, dorsal vagal, trigeminal, gracile and cuneate nuclei. Less severe change in oculomotor and ambiguous nuclei. Spinal cord: severe retrograde cell change in anterior horn cells.
11. E. G—, female, aged 32	12 years. Schizophrenia. Uraemia. Sub-pellagrous state	Loss of weight. Diarrhoea. "Sunburn" arms and legs	"	" Dietary "	Severe retrograde cell change in Betz cells,

TABLE I.—*cont.*

Case.	Length of stay in hospital and diagnosis.	Somatic manifestations.	Neurological manifestations.	Treatment.	Histological findings.
12. D. M. N—, female, aged 44	2 months. ? Pellagra	Loss of weight. Diarrhoea	Confused and drowsy. Dysarthria. Spastic weakness of lower limbs. Extensor plantar responses	—	Severe retrograde cell change in Betz cells and nerve cells of pontine nuclei. Moderate retrograde cell change in dorsal vagal, gracile and cuneate nuclei. Spinal cord: severe retrograde cell change in anterior horn cells. Myelin stains: no abnormality. With fat stains droplets of free fat and many fat-laden granular compound cells were seen in the lateral columns of thoracic and lumbar regions (Fig. 4).
13. P. R—, female, aged 32	10 years. Schizophrenia. Pellagra	Loss of weight. Diarrhoea. Dermatitis of legs and hands	"Epileptiform attacks." Spastic paraplegia	—	Severe retrograde cell change in Betz cells, less marked in nerve cells of oculo-motor pontine, dorsal vagal, cuneate and gracile nuclei. Spinal cord: moderate retrograde cell change in anterior horn cells. Degeneration of crossed and uncrossed pyramidal tracts at all levels (Fig. 3 <i>a</i> , <i>b</i>), ascending as far as the peduncles of the midbrain. Fasciculus gracilis slightly demyelinated in the lumbar region.
14. P. V—, female, aged 53	5 years. Acute confusional insanity. Pellagra	Diarrhoea, stomatitis. Dermatitis of face and hands on exposure to sun	"Epileptiform attacks." Confused, disorientated	Nicotinic acid	No abnormality in the nervous system.

TABLE II.

Case.	Onset of loss of weight.	Onset of diarrhoea.	Onset of dermatitis.	Date of death.
H. C—	1934 with fluctuations until date of death	September, 1941	Erythema of face, 1934	24.iii.42
R. H—	? January, 1938	? June, 1938	20.x.38	27.x.38
J. M. J—	1943	April, 1945	January, 1945, dermatitis of lips, chin and chest	1.v.45
E. K—	1941	December, 1943	"Sunburn" legs, 1941. Erythema hands, neck and feet, 1944	28.vii.44
B. P—	? Early 1944	December, 1944	Erythema face, March, 1945	5.vi.45
N. W—	1932 with fluctuations	November, 1932, recurrent attacks until death	1940: "rash" of hands, chest and limbs	2.v.41
J. H—	1937	1938, recurrent attacks	Dermatitis face, neck and hands, July, 1939	4.viii.39
V. C. T—	1942	September, 1943	Dermatitis arms and trunk, 1938	27.ii.44
A. H—	1935	September, 1936	Dermatitis of face, chest and hands, May, 1936	21.ix.36
D. M—	March, 1940	June, 1940	Dermatitis of hands, 1940	11.ii.41
E. G—	1936	January, 1937	"Sunburn" of hands, June, 1940	2.x.41
D. M. N—	1937	June, 1938	None recorded	1.viii.38
P. R—	1936	Not recorded	Sunburn, 1937, 1943	13.xi.45
P. Y—	1938	July, 1938, recurrent attacks	Sunburn, August, 1938	18.x.43

cells, or in the remainder of the C.N.S. In order of frequency the following groups of cells showed a retrograde cell change: pontine nuclei (13 cases) (Fig. 2); dorsal vagal nuclei (11 cases); gracile and cuneate nuclei (11 cases); nucleus ambiguus (7 cases); descending trigeminal nucleus (5 cases); oculomotor nuclei (4 cases); basal ganglia (3 cases); vestibular nuclei (2 cases); and reticular and arcuate nuclei (1 case). The spinal cord was available for examination in only six cases. The anterior horn cells showed a severe degree of retrograde cell degeneration in 4 of these cases, in one a moderate change, and in the remaining case the anterior horn cells were normal. It is noteworthy that some groups of motor cells—the cells of the hypoglossal and facial nuclei, for example—were seldom affected. It was particularly noticeable how invariably the cellular structure of the hypoglossal nuclei was preserved. A further feature of some interest is that of the groups of neurones affected, the cell change varied from cell to cell. Thus, for instance, some Betz cells might show a severe retrograde cell degeneration, whilst others in the same area would be less severely affected. It is important to point out that no axonal abnormalities were detected in any of the cases.

The remaining neurones of the different cortical layers remained histologically intact. The nerve cells of the thalamus and hypothalamus were unaffected.

In the cerebellum no abnormality of any cell groups was noted; the Purkinjé cells, although amongst the largest neurones of the central nervous



FIG. 1.—Betz cell, showing retrograde degeneration. Note eccentric nucleus and dissolution of Nissl bodies. (Case 3.) Nissl. $\times 400$.

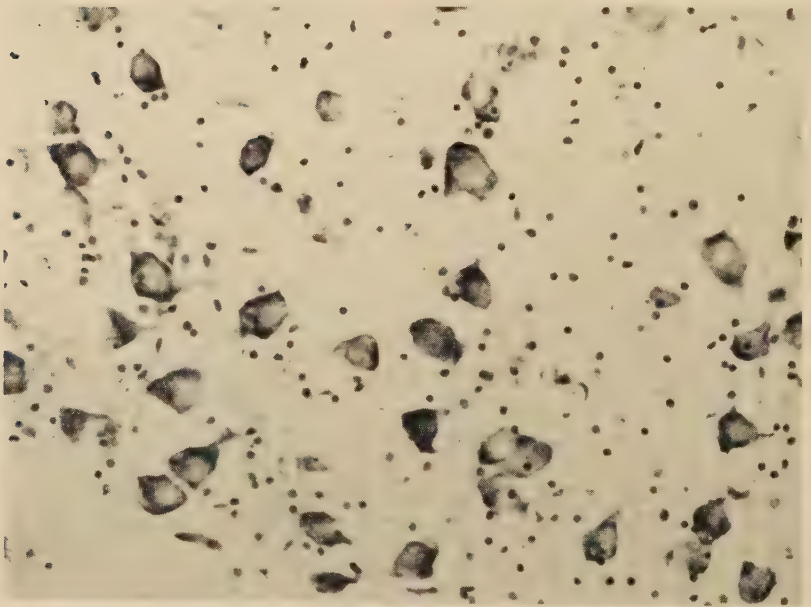


FIG. 2.—Pontine nuclei. Nerve cells showing retrograde degeneration. (Case 3.) Nissl. $\times 250$.

system, were well preserved, as were the granules, and the cells of the cerebellar nuclei.

The hemispherical and cerebellar white matter showed no changes. The blood vessels were normal in 11 cases; in the remaining 3 patients a hyaline change was present in the walls of the arterioles. In only one case was peripheral nerve available for examination—no abnormality was present. The optic nerve and chiasm were examined in three cases, with completely negative findings.

In the six cases in which the spinal cord was available for examination a degeneration of the lateral column was present in three. In the first of these cases (Case 2) a lateral column degeneration alone was present; in the second case (Case 12) no apparent alteration could be detected in sections stained for myelin, but in Herxheimer preparations compound granular cells filled with lipoids, and some droplets of free fat, were present in the lateral columns (Fig. 4). In the third case (Case 13) the degeneration of the pyramidal tracts could be traced upwards through the brain stem as far as the midbrain, and both direct and crossed pyramidal tracts were affected (Fig. 3*a* and *b*). In addition to this case there was a slight demyelination of the inner zones of the fasciculi gracilis in the lumbar region.

DISCUSSION.

The neuropathology of pellagra has been extensively studied. In 1915 Raubitschek, from an analysis of over 1,400 references to pellagra, concluded that the most significant pathological finding was a retrograde cell change, affecting particularly the Betz cells of the motor cortex. The large pyramidal and medium-sized cortical neurones, the nerve cells of the thalamus and of the bulbar nuclei also showed this change, as did the anterior horn cells. The Purkinjé cells were, however, invariably normal in appearance. This retrograde cell change was considered to be the primary evidence of pellagra, the fibre tract degeneration and polyneuritis to be secondary in nature. Whilst most authors stressed the importance of this retrograde cell change, considerable attention was directed toward the tract degenerations found in the spinal cords of many "pellagrins." The dorsal and lateral columns were mostly commonly affected. Greenfield and Holmes (1939), reporting a clinico-pathological study of one case of pellagra, described a pronounced degeneration in the fasciculus gracilis, less pronounced in the spino-cerebellar tracts, and of only slight degree in the crossed and uncrossed pyramidal tracts. In 1942, Hsü, in Peiping, published an excellent review of the pathological anatomy of the human nervous system in avitaminosis. In a series of 13 Chinese soldiers suffering from malnutrition he described degeneration of the dorsal spinal ganglia, posterior nerve roots and posterior columns. In 11 of the 13 cases the fasciculus gracilis was involved, and in 10 of these the fasciculus cuneatus was also affected, but to a lesser degree. This posterior column degeneration was more marked in the upper dorsal region of the cord than in the lower segments. In only one case was lateral column degeneration associated with the posterior column change, and then it was in the early Marchi

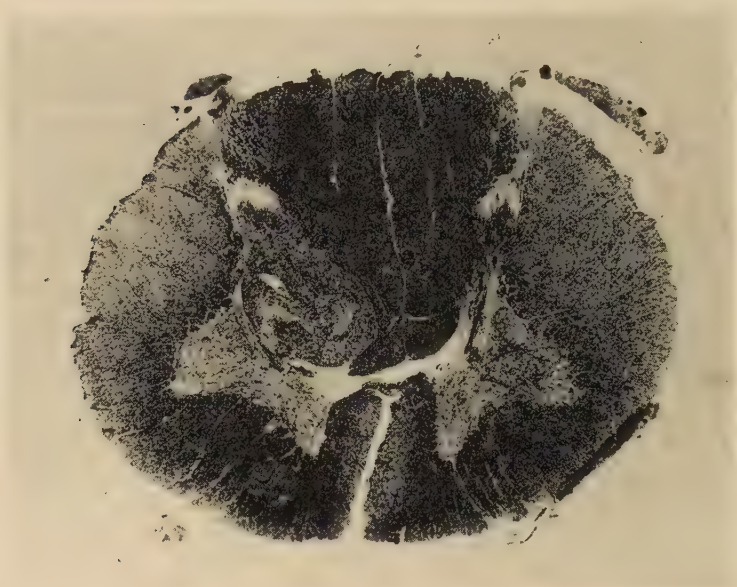


FIG. 3(a).

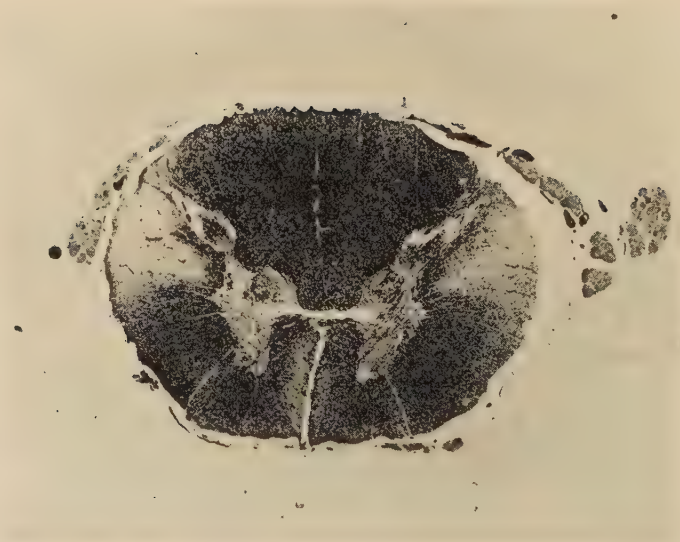


FIG. 3(b).

FIG. 3.—(a) Spinal cord showing degeneration of crossed and uncrossed pyramidal fibres (C 6). (Case 13.) Heidenhain. $\times 9$.

(b) Spinal cord showing degeneration of crossed and uncrossed pyramidal fibres (T 10). (Case 13.) Heidenhain. $\times 9$.

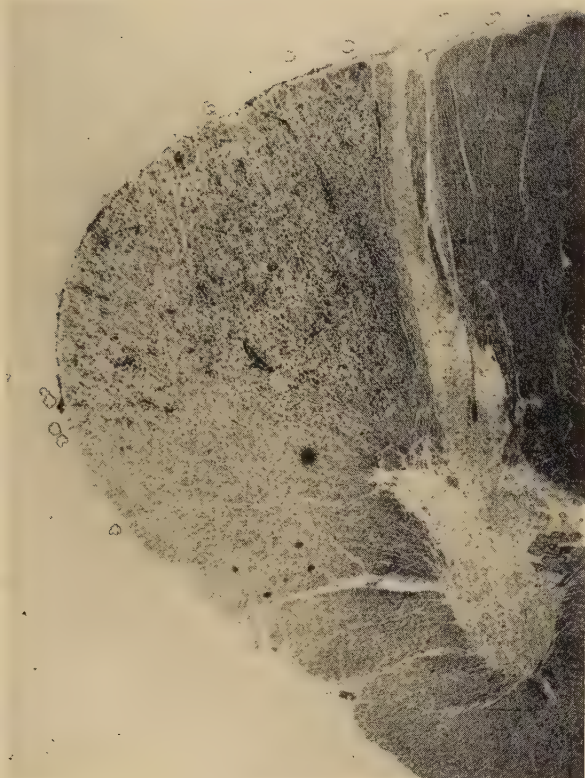


FIG. 4.—Spinal cord showing fatty change in lateral column (T 6). (Case 12.) Scharlach R. $\times 25$.

stage of degeneration. A retrograde cell degeneration was present in all his cases, affecting the Betz cells in particular. It is noteworthy that during the terminal illness only one of these 13 cases showed the cutaneous manifestations of pellagra.

The clinical study of groups of prisoners of war suffering from malnutrition, both in the Middle East (Spillane and Scott, 1945; Spillane, 1947) and Far East (Denny Brown, 1947), has conclusively established that a spinal cord syndrome in many respects identical with the spinal syndrome previously described as pellagrous may occur as an isolated manifestation of dietary deficiency. It is now quite clear that degeneration of the white matter in the spinal cord is by no means constant in "pellagra," and is not an integral feature of the condition.

Lesions of the cranial nerves, in particular of the olfactory, optic, trigeminal, auditory and vagus nerves, although well recognized clinically in nutritional disorders, have received little pathological study. Harris (1912) had observed pellagrins in whom the sense of smell was decidedly lessened, and in groups of prisoners of war suffering from malnutrition in the Middle East, Spillane and Scott (1945), noted the occasional presence of anosmia. Sensory change in the trigeminal area have been recognized by the Japanese for many years

and by other authors (Willcox, 1916; Kagawa, 1938; de Wardener and Lennox, 1947). The cranial nerves most commonly affected in nutritional disorders are the optic nerves, the auditory nerves, and the vagi. Diminished hearing in pellagrins was recorded by Roncorini (1890), and has been described in dietary deficiency states by many authors since that date.

In the early literature of pellagra visual disturbances were frequently remarked. Calderini (1847), in a study of over 1,000 cases of pellagra, noted amblyopia or diplopia as a symptom in 48 per cent. of the males and 72 per cent. of the females. The first precise ophthalmic description of visual disturbance in deficiency states, however, came from Japan (Kono, 1895; Komoto and Aoki, 1903). In spite of extensive clinical studies the pathological changes in the cranial nerves remain obscure. Kagoshima (1918) examined pathologically 5 cases of "beri-beri amblyopia with central scotoma." In each he found a well-marked and limited atrophy of the fibres in the external segment of the optic nerve. Scott (1918) described a widespread degeneration distributed along practically all the fibres of the optic nerve in cases of acute pellagra. Degeneration of the vagi was noted by Zimmerman *et al.* (1934) in cases of "alcoholic pellagra."

A peripheral neuritis has been considered to be more characteristic of beri-beri than pellagra. Peripheral nerve changes, however, have been frequently reported in association with pellagra. The earliest pathological studies were those of Déjerine (1881), who found extensive degeneration of the myelin sheaths. Greenfield and Holmes (1939) noted degeneration of the entering posterior root fibres, particularly in the lumbar region, and here some degeneration of the anterior roots was also seen. Wilson (1940), in a study of 13 cases of pellagra, reported practically constant peripheral nerve changes, ranging from swelling or thinning of myelin sheaths, fragmentation of axones, oedema of nerve fibres and bundles, and thickening of the epi- and perineurium. Hsü (1942) recorded degeneration of both anterior and posterior nerve roots, and of nerve trunks.

Changes in the blood vessels and the glia in cases of "pellagra" have proved of relatively little importance. Kozowsky (1912), observed swelling of the intima, and hyaline degeneration of the walls of many small vessels in the brain and spinal cord, and similar changes have been noted by other authors (Winkelman, 1926; Pentschew, 1928; Hsü, 1942). These changes have been, however, by no means a constant feature of cases described as pellagra.

Neuroglial changes have been recorded by the minority of authors. Kozowsky (1912) noted a widespread proliferation of neuroglia, both fibres and cells, throughout the nervous system, but Pentschew (1928) observed little change. Wilson (1940), and the majority of the authors previously mentioned, subscribe to this latter view.

It is thus apparent from a review of the neuropathology of cases described as suffering from "pellagra" that the many recorded changes mirror the multiplicity of syndromes embraced by the term. Biochemical and clinical studies have clarified the problem to some extent, and a clinico-pathological correlation may now perhaps be attempted. From the findings presented

here, and a review of the relevant literature, it seems clear that one of the syndromes previously described under the title of pellagra presents a characteristic clinico-pathological picture. Clinically it is manifested by mental changes, loss of weight, diarrhoea, and a dermatitis of those parts of the body exposed to sunlight. The only constant neuropathological correlate of this syndrome is a retrograde cell degeneration affecting certain groups of nerve cells throughout the nervous system. The Betz cells in particular are invariably affected, and indeed, this affection of the Betz cells is pathognomonic of the syndrome. It is suggested that the term "pellagra" could be reserved, with some justification, for this condition alone.

Secondly, many clinical and pathological studies show that a spinal cord syndrome may result from a different type of nutritional deficiency, occurring alone, or in combination with other deficiency syndromes. The posterior and lateral columns of the cord are particularly affected, and give rise to a clear-cut pathological and clinical picture.

Thirdly, many of the complications of "pellagra," such as blindness and deafness, are again separate syndromes, separate in aetiology, and appearing as well recognized clinical entities. Retro-bulbar neuropathy and deafness are, however, particularly linked with the spinal cord deficiency syndrome.

Lastly, peripheral nerve degeneration is a common feature of nutritional deficiency—either dominating the clinical picture, when it is labelled beri-beri, or in combination with the cord syndrome, the cranial nerve palsies, or mental changes. There is much evidence to show that a specific food factor (Denny Brown, 1947) is concerned with the physiological maintenance of the peripheral nervous system.

CONCLUSIONS.

1. The term "pellagra" is no more than a generic title, embracing several nutritional deficiency syndromes of differing aetiology.
2. One of these syndromes has been studied clinically and pathologically.
3. Clinically, the syndrome was characterized by loss of weight, diarrhoea, dermatitis of exposed surfaces, and mental changes.
4. A retrograde cell degeneration of the Betz cells was the only constant pathological finding.

The cells of the pontine, dorsal vagal, gracile and cuneate nuclei also showed a similar change, but were less constantly affected than the Betz cells.

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SPECTROSCOPIC AND PHOTO-ELECTRIC OXIMETRY IN SCHIZOPHRENIA AND OTHER PSYCHIATRIC STATES.*

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INTRODUCTION.

THE purpose of this paper is to outline the application to various psychiatric conditions of a test which measures peripheral capillary oxygen saturation and to discuss the significance of the findings. It is convenient to commence with a brief review of some previous work concerning the relevance of anoxaemia to psychiatry.

The role of anoxaemia in producing mental symptoms has long been recognized. Haldane (1922) and Barcroft (1925), amplifying and extending the original observations of Paul Bert (1878), demonstrated the close association between psychic integration and oxygen availability. Listing the symptoms which chronic anoxaemia could produce, Haldane mentions dulling of the sensorium, early memory loss, gradual impairment of judgment, onset of irrational and fixed ideas, affective lability with uncontrolled emotional outbursts and often with initial euphoria and later depression, impaired muscular co-ordination, irresponsibility, handwriting and speech changes. Though the subject may notice his impaired co-ordination or his changed handwriting, he is usually convinced that he is perfectly sane and reasonable. Furthermore, he cannot properly interpret his sensory impressions, and he tends to repeat spoken or written words. Transforming these observations into psychiatric terms, Haldane might have said, as McFarland (1932) and Hoskins (1946) have pointed out, that the chronic anoxaemic subject presented many of the symptoms characteristic of schizophrenia.

In a similar fashion numerous writers have attested to the frequency with which schizophreniform reactions result from the wide variety of conditions which have anoxaemia as their common factor. As examples may be noted: carbon monoxide intoxications (Kant, 1926), various other gases (de Jong, 1934), nitrous oxide anaesthesia (Fletcher, 1945), chronic mountain sickness (Monge, 1937), bulbo-capnine intoxication (de Jong and Baruk, 1930), chronic infection (Wimmer, 1937), and influenza (Menninger, 1928; Kamman, 1930), and the many reports dealing with tuberculosis and with surgical procedures. Sometimes it is possible to differentiate these psychiatric symptoms as

* This work was done during the tenure of a Nuffield Foundation Fellowship in Medicine (Psychiatry).

organically determined ; at others they present as apparently nuclear cases of schizophrenia.

As with schizophrenia, so with many "idiopathic" psychiatric syndromes. Affective disorders, both manic and depressive, are readily produced under conditions of low oxygen pressure, while symptoms reminiscent of various neurotic states are reproducible in a similar fashion (McFarland, 1932 ; Gellhorn and Joslyn, 1936).

Such observations suggest that it is pertinent to inquire into the oxygen metabolism of psychiatric patients, but the workers who have already attempted such a study in cases of schizophrenia have met with conflicting and often disappointing results. Hoskins (1932, 1946) has shown conclusively that the oxygen consumption of patients with schizophrenia is significantly low compared with normals when measured under basal conditions. There seems little doubt that this is the case, for his work was carefully controlled and has been amply confirmed. Yet, if there is defective oxygen uptake in schizophrenia, then there should also be defective oxygenation of the tissues. A satisfactory demonstration of such tissue hypoxia has not been made. Although Katzenelbogen (1944), in an examination of arterial and venous blood from the cranial cavity of schizophrenics, concluded with reservations that intracranial oxygen metabolism may be lower in schizophrenics than in normals, Looney and Freeman (1938), in a study of the oxygen and carbon dioxide content of arterial and venous blood in 112 schizophrenic patients and 67 controls by Van Slyke's method, could find no differences between the means of the controls and the psychotics. Kety and his co-workers (1948) repeated this work using the nitric oxide method and achieved the same result. Greville (1945), comparing the figures of Wortis (1940) for mean arterio-venous differences in 53 schizophrenics with those of Gibbs (1942), who examined 50 normal young men, concludes that cerebral arterio-venous differences are not abnormal in schizophrenia. Myerson and Halloran (1930) studied the oxygen content of blood from the internal jugular vein in 20 schizophrenic patients and found it essentially within normal limits, only 6 patients having a venous oxygen tension below 10 volumes per cent. In Segal and Hinsie's (1926) series of 14 cyanosed schizophrenics, similarly, the mean oxygen and carbon dioxide tensions were normal. A solitary, but recent, Russian paper challenges this mass of evidence. Using a histochemical technique, Tsikhanshkaya (1948) found that the haemoglobin of most of her 30 cases of schizophrenia showed a defective oxygenation, as compared with a group of 60 healthy controls.

Studies on the velocity of blood flow in schizophrenia have also been disappointingly inconclusive. Although Freeman (1938) claimed a slower rate and greater variability for 32 schizophrenics as compared with 29 normals, this was not confirmed by Finesinger (1938), employing the same sodium cyanide technique on 55 psychotics. Finesinger found in his patients that the average arm to carotid circulation time, the average crude pulmonary circulation time and the calculated average venous circulation time were all within the normal limits. Against this the work of Rosenbaum (1942), who measured the intracranial blood-flow by Ferris' (1941) method and found no significant diminution

of intracranial blood flow in schizophrenic subjects, but a large standard deviation. A markedly diminished peripheral blood-flow has also been found in 29 schizophrenics by Abramson (1941) using a plethysmographic technique.

More general agreement is found in blood volume studies. Looney and Freeman (1935) showed a significant reduction in their series of schizophrenic subjects when the blood volume was compared with the body surface area; Finkelman and Haffron (1937) confirmed this finding. Apparently when compared with body weight, the blood volume of schizophrenics is normal.

Quastel (1945) has stated that the cerebral cortex is so sensitive to anoxaemia that localized changes may produce psychiatric symptoms with very little overall change in cerebral metabolism. It seems evident, therefore, that if we are to find objective demonstration of such anoxaemia in a syndrome so loosely knit and presenting such diverse clinical features as that of schizophrenia, we shall not do so by such gross technique as a study of arterio-venous oxygen differences in the blood of large arteries and veins. Oxygen is of little use in these situations. It is the capillaries, those blood vessels that are in intimate relationship with the oxygen of the blood on the one hand and the needs of the tissues on the other, that are *effectively* concerned with oxygen transport and availability. The capillary is the analogue in oxygen metabolism of the anterior horn cell of neurology in that it is the final common path for the supply of oxygen to the tissues. Indeed, as Haldane (1922) has pointed out (p. 277), "When once the fundamental fact is grasped that the general flow of blood throughout the body is correlated with the gas pressure in the capillaries, the whole physiology of the circulation appears in a new light." He emphasized that the regulation by the tissues of the amount of blood supplied to the heart depends "to an overwhelming extent" on a dual control by the oxygen pressure and pH of the blood of the systemic capillaries, a conviction recently confirmed by oximetry studies (Penneys and Thomas, 1949).

It would appear possible, therefore, that to follow up this early lead and examine the oxygen availability of the blood of the capillary system, rather than of the larger vessels, might prove more rewarding. Such has been found to be the case. The present paper is concerned with an oximetric study of "effective capillary oxygen saturation," i.e., that fraction of dissociable oxy-haemoglobin the oxygen of which is available to the tissues.

SPECTROSCOPIC OXIMETRY BY THE REDUCTION TIME (RT) TECHNIQUE.

In 1946, in a series of papers, Ray and his co-workers re-introduced a method of measuring capillary oxygen saturation spectroscopically. It involved few materials, little discomfort and no trauma to the patient. It was so rapid that a series of determinations could be run on a subject with minimal co-operation from him in a matter of minutes. It was satisfactorily accurate (correlation coefficient with alveolar oxygen tension was plus 0.87, and with oxygen consumption, as measured by the B.M.R., minus 0.67) and it gave closely approximated test-retest results. Ray, Johnson and Ray also measured the response of the reduction time to the stress of breath-holding,

and from their data derived an index—the “RT score”—which represented the difference, in seconds, of the RT and the RT as measured under the stress of minimal breath-holding, expressed as a percentage of the RT at rest. This RT score, they claimed, was a reliable index of “physiological efficiency” in the various groups of U.S. Army personnel employed as their subjects. They showed that a score of plus 10 or more was given by trained, fit men, while physically ill patients and convalescents from a Military Hospital had a score of less than plus 10. Training, similarly, had the effect of raising the score from a mean of 27 to a mean of 30.4—a statistically significant difference.

Ray's technique involved the construction of a special metal holder for the light source and spectroscope and the use of an area of skin on the back of the hand for the determination. The presence of many veins in this area led sometimes to abnormally high RT values, and necessitated a preliminary occlusion to ensure that the RT of the actual capillaries was being studied. The present work reported here obviates these difficulties by employing a different method of illumination and by using the capillaries of the finger-nail fold for study.

Experimental procedure.—Apparatus consisted of a pocket prismatic spectroscope held in a retort stand clamp and focused, using as narrow a slit as practicable, on the skin of the nail fold of the ring finger of the left hand of the subject, who grasped a carved hand holder mounted rigidly on a stand. The area was illuminated by a point source of light provided by a 25-watt, 50-volt projector lamp energized from the mains through a step-down transformer. The light was focused by a condenser to provide a pin-point on the nail fold skin of about 0.25 inch in diameter. The skin site was prepared beforehand by rubbing it with a dry cloth and inuncting 2 per cent. histamine ointment (British Drug Houses, Ltd.) into it. A sphygmomanometer cuff was wrapped around the left upper arm, and connected by a length of rubber tubing to a Winchester quart glass bottle provided with a mercury manometer inserted through its rubber bung and a rubber bulb for increasing its internal pressure to approximately 300 mm. Hg. A clip on the tube connecting the pressure bottle with the cuff enabled air under pressure to fill the cuff in a negligible time interval—rather less than 1 second.

A reading was taken after the subject had been sitting comfortably for some minutes with his prepared hand in position, the cuff in place, and the pressure bottle pumped up. The clip was opened and at the same time a stop-watch was started. The oxyhaemoglobin absorption bands, clearly visualized in the orange and green (Fig. A) after focusing the spectroscope on the illuminated skin area, disappeared 15 to 75 seconds after circulatory occlusion, and the time taken for such disappearance to occur was taken to represent the reduction time. A series of readings was always taken, the RT settling after 1–2 readings to a constant figure.

The RT under stress was determined first by finding the total time during which the subject could hold his breath after a normal inspiration, and then by repeating the RT measurement with the subject holding his breath in a similar fashion for a tenth of this total breath-holding time. A time of 3 seconds was taken as the minimum stress in view of the fact that some breath-

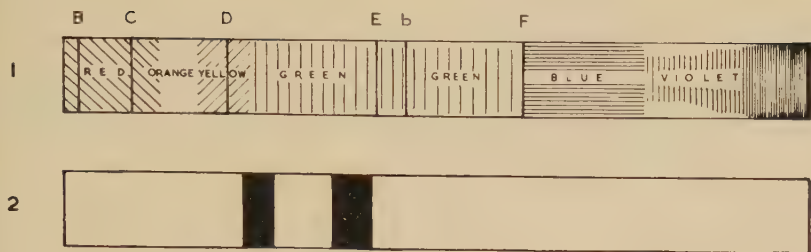


FIG. A.—Showing position of spectroscopic absorption bands of oxyhaemoglobin as visualized during spectroscopic oximetry and as compared with the solar spectrum.

holding times among the schizophrenia population especially were so short that 10 per cent. of them would have represented negligible values. Most subjects came into the range of 3–6 seconds for this percentage of total breath-holding time.

In order to guard against possible climatic and other possible environmental variables, the subjects and patients whose results are reported here were examined in parallel batches and over a period of many weeks. No differences were noted which could be attributed to changes in external temperature or barometric pressure. All subjects of the investigation, both controls and patients, were apparently physically healthy at the time of examination.

CLINICAL MATERIAL. (RT SPECTROSCOPIC OXIMETRY.)

This consisted of the following groups of subjects :

(a) 112 *normal soldiers* all drawn from a nearby R.A. Depot. The only criteria for their selection were that they should be of average intelligence, and not have given evidence of having broken down psychiatrically during their army service. They were, of course, all males, and their ages ranged from 18 to 43, with a mean of 26.1 years. They were not volunteers for this investigation, they came from all walks of civilian life and, since they included many conscripts, they formed a fairly representative sample of the average man within the limits of this selection.

(b) 64 *neurotic subjects*, the majority of whom were army personnel. They were all "constitutional" neurotics who had broken down during their Service career and whose illness was sufficiently serious to warrant invaliding from the Service. They comprised 6 acute anxiety states, 20 chronic anxiety states and 23 hysterics. A small group of 15 hospital patients was also examined ; they represented 5 chronic anxiety states and 10 hysterics. The army group was all male ; the hospital group consisted of 4 males and 11 females. Combined ages ranged from 18 to 42, with a mean of 25.0 years.

(c) 67 *schizophrenic patients* : 39 of these were drawn from the wards of the Bethlem Royal and Maudsley Hospitals and 28 from Cane Hill Hospital. The former group were, in the main, younger subjects, their illness was reasonably acute and deterioration had not set in. The latter group included patients some of whom showed gross degrees of deterioration. All patients in both

groups had been seen by at least two psychiatrists and their diagnoses confirmed. These diagnoses provided the following sub-classification :

- (i) 51 "constitutional" or "process" schizophrenics including 6 cases of dementia praecox simplex, 7 cases of catatonic schizophrenia, and 38 cases of hebephrenia.
- (ii) 16 "paranoid" schizophrenics.

The mean age of the "constitutional" schizophrenic patients was 31.1 with a range of 16 to 55 years ; they included 26 males and 25 females. The mean age of the "paranoid" group was 33.5 with a range of 20 to 60 years ; there were 5 males and 11 females. Most representatives of both groups had completed courses of insulin coma treatment or electrical convulsive therapy at varying times prior to examination but without substantial improvement in their psychiatric condition. Poor co-operation on the part of 4 deteriorated patients accounted for their RT scores being absent.

(d) 22 *patients with affective disorders* : These were all hospital patients and, save for one manic, were examples of various types of depressive states. They included 10 subjects with endogenous forms of depression, 5 with reactive and 6 with tension or hysterical depressions. Most of the endogenous group were examined towards the end of a course of electro-convulsive therapy and were in varying phases of recovery. There were 9 males and 13 females, and the ages ranged from 18 to 55 with a mean of 31.4 years.

(e) 17 *patients with psychopathic personality* : 10 of these were army personnel, the remaining 7 being hospital patients. Ages ranged from 18 to 55 with a mean of 28.7 years ; there were 14 males and 3 females. They were subdivided into two main categories ; 5 predominantly aggressive psychopaths and 12 predominantly inadequate psychopaths. The latter group included 5 homosexuals.

(f) 13 *patients with miscellaneous organic cerebral disorders* : These hospital patients included 5 epileptics, 3 post-encephalitics, 2 pre-senile dementias, 1 head injury, 1 alcoholic Korsakoff psychosis and 1 spastic paraplegia. All had complicating and varied secondary psychiatric symptomatology. There were 6 males and 7 females. Ages ranged from 21 to 65, with a mean of 37.2 years.

PHOTO-ELECTRIC OXIMETRY BY THE MILLIKAN ANOXIA PHOTOMETER.

One of the potential objections to spectroscopic peripheral oximetry would seem to lie in the fact that such a technique measures capillary oxygen saturation of an area notoriously often cyanotic in certain types of schizophrenia, and hence perhaps not representative of oxygen saturation elsewhere in the body. It was considered desirable therefore to confirm these RT results by another method of oximetry. The instrument described by Millikan (1942) was chosen for this, since the principle on which it operates is similar to that upon which the reduction time relies. The Millikan oximeter depends upon the fact that it is possible to measure, by means of a series of photo cells and a red filter, the change in transmission of light between oxyhaemoglobin and

reduced haemoglobin, and such a change can be calibrated in terms of saturation of haemoglobin with oxygen.

The efficient operation of this instrument is dependent upon adequate vasodilatation of the part examined, i.e., the lobe of the ear, and this is obtained through the application of warmth by a small constant current lamp embodied in the ear-piece. The accuracy of the instrument is of a high order, Millikan claiming an error of not more than ± 5 per cent. against arterial puncture measurements in the upper range.

Through the kindness of Professor T. Rennie of the Payne Whitney Clinic and the co-operation of Dr. H. L. Flowers and the staff of the Bronx V.A. Hospital, New York, it was possible to investigate, in addition to the English patients already mentioned, a further series of 20 schizophrenics, together with an isolated example of involuted melancholia and six healthy, mentally stable, control subjects. This American material, though small numerically, was handled rather more extensively than the British group, in that not only was the RT measured at frequent intervals, but also a continuous oximetric record with the Millikan instrument was obtained for each patient over the period of an hour's psychiatric interview. The results, which amply confirmed the original RT determinations, are discussed below.

RESULTS.

These may be studied in detail in Tables I-IV and in Figs. B and G. In view of the fact that the age ranges and mean age values showed some variation in the seven groups studied, it was considered advisable to include a graph (Fig. C), in which age is plotted against RT for the 112 individuals of the control group. From this graph it can be seen that absolutely no correlation exists between these two variables. Similarly a glance at the histogram (Fig. D) shows that neither sex, age, type of onset nor duration of illness bear any relationship to RT values. The statistical significance of factors which *do* show correlations is indicated in the Tables. Standard deviations have been worked out for the means of all the 7 major diagnostic groups (Table I), and an analysis of variance (Table II) shows that the F ratios for both RT and RT score are significant down to the 1 per cent. level of confidence.

TABLE I.—*Showing Basic Data on 295 Individuals with Various Psychiatric Syndromes.—English Series.*

Psychiatric group.	Age range (years).	Mean age (years).	Sex.		N.	Mean RT.	S. D. RT.	N.	Mean RT +.	Mean RT score.	S. D. RT Sc.
			M.	F.							
Controls . . .	18-43	26.1	112	0	112	41.143	8.904	112	35.1	+14.625	10.741
Neurotics . . .	18-42	25.0	53	11	64	37.969	11.178	64	38.2	-0.859	11.447
Psychopaths . . .	18-55	28.7	14	3	17	40.706	12.864	17	36.9	+6.706	13.610
Depressives . . .	18-55	31.4	9	13	22	42.955	17.020	22	36.2	+14.182	16.555
Process schizophrenics . . .	16-55	31.1	26	25	51	21.157	2.428	47	16.7	+10.000	13.296
Paranoid schizophrenics . . .	20-60	33.5	5	11	16	33.938	12.375	15	27.6	+10.667	17.791
Miscellaneous organic cases . . .	21-65	37.2	6	7	13	56.846	15.721	11	42.8	+15.636	19.694

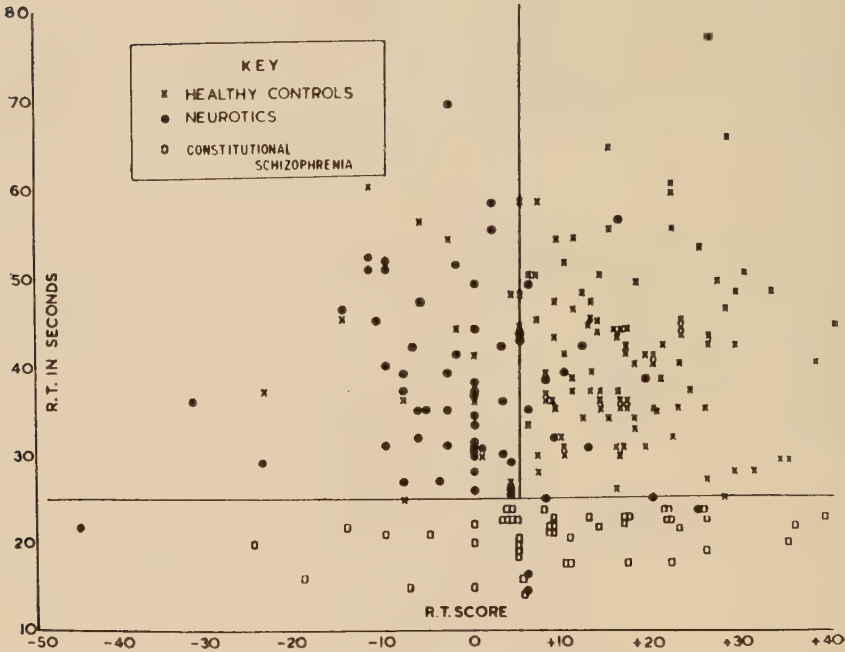


FIG. B.—Differentiation of constitutional schizophrenic and psychoneurotic patients from each other and from healthy controls by means of spectroscopic oximetry combined with the RT score resulting from effect of breath-holding stress.—English series ; maximal differentiation is obtained by shifting the critical RT score from + 10 to + 5 as shown. (Compare Prediction Table IV.)

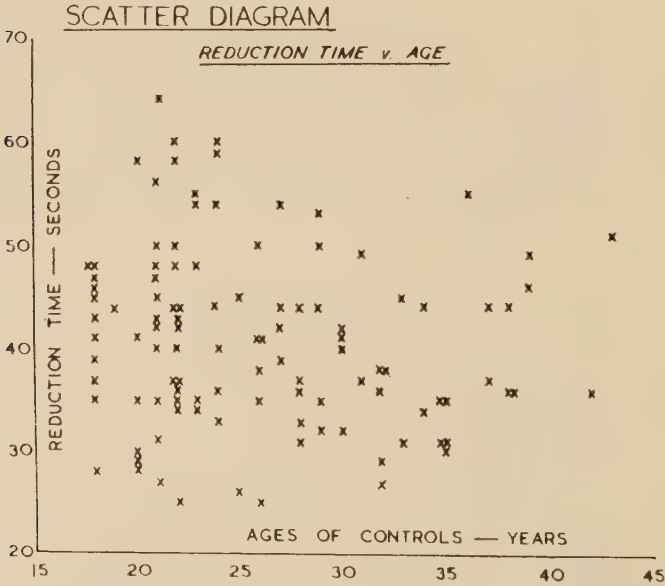


FIG. C.—Graph showing lack of influence of age on arterial oxygen saturation levels as determined spectroscopically.—English series : control groups, age range 18-43 years.

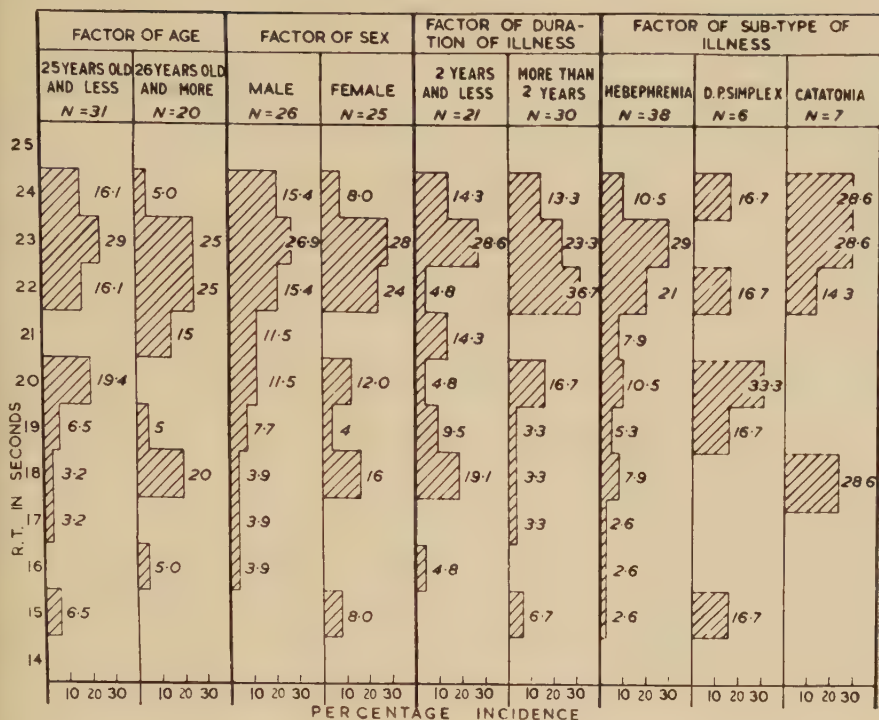


FIG. D.—Histograms showing relationship of various factors within the constitutional schizophrenic group to the arterial oxygen saturation levels.—English series; spectroscopic oximetry.

TABLE II.—Showing Statistical Results of a Test of Significance for Spectroscopic Oximetry when Controls and all Abnormal Psychiatric Groups are Compared.—English Series.

Analysis of Variance for RT in Seven Groups (D.f. = N - 1).

	Source.	Degrees of freedom.	Deviance.	Mean square.	F. ratio.
RT	Between groups	6	21,017.859	3,502.976	32.5864 $(r^2 = 0.404)$ Sig. at 1 per cent. level
	Within groups	288	30,959.511	107.498	
	Total	294	51,977.370		

Analysis of Variance for RT Score in Seven Groups (d.f. = N - 1).

RT score	Between groups	6	10,851.805	1,808.634	10.9952 $(r^2 = 0.190)$ Sig. at 1 per cent. level
	Within groups	281	46,222.664	164.493	
	Total	287	57,074.469		

Fig. E represents a correlation study of 285 simultaneous observations of RT and Millikan oximeter and enables RT values, in seconds, to be expressed in terms of per cent. oxygen saturation. It would appear that 92.1 per cent. of capillary blood oxygen content (RT = 25 secs.) is the oximetric critical low level for functional normality under the conditions of these experiments. The correlation coefficient was calculated from these figures and found to

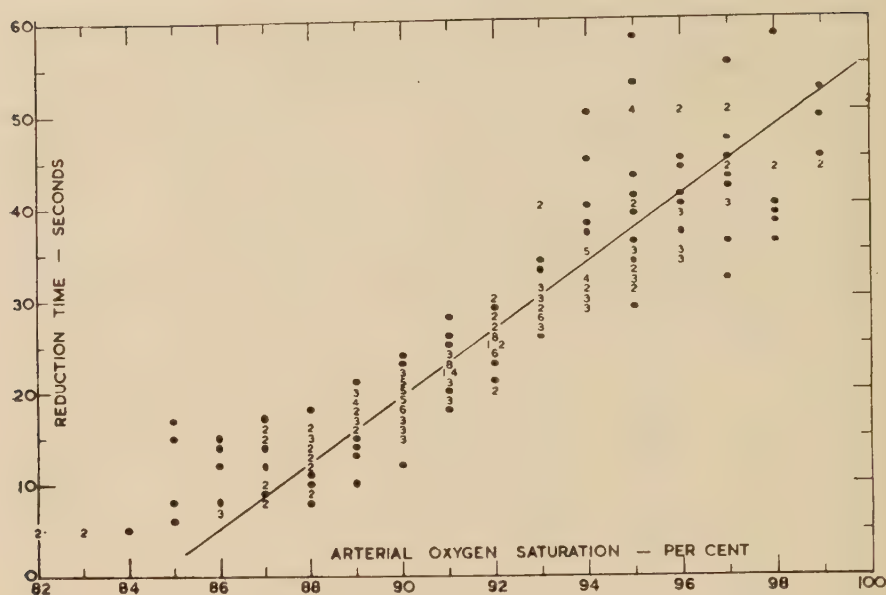


FIG. E.—Calibration graph showing scatter when simultaneous observations are made by both spectroscopic and photo-electric technique of oximetry.—American series. Correlation coefficient (r) = 0.916. Regression equation for prediction of arterial oxygen saturation per cent., (X), from RT secs., (Y): $\bar{X} = 84.6 + 0.3Y$.

represent an r of + 0.916. Substitution of reduction time values (Y) in a regression equation* enables the percentage arterial oxygen saturation (X) to be calculated from the simple formula, $\bar{X} = 84.6 + 0.3Y$.

TABLE III.—Comparing Control Group Results with Differential Analysis of Mean Scores in Sub-groups of Main Psychiatric Classifications. Means correct to one decimal place for convenience of comparison.—English Series.

	Diagnosis.	Number.	Mean RT.	Mean RT. +	Mean RT score.
	Controls	112	41.1	35.1	+14.6
Psychoneurosis	{ Acute anxiety states	6	40.7	39.3	+2.2
	{ Chronic anxiety states	25	39.6	40.2	-2.2
	{ Hysterics	33	36.2	36.6	-1.3
Psychopathic personality	{ Aggressive psychopathy	5	37.6	34.8	+8.8
	{ Inadequate psychopathy	12	42.0	37.8	+5.8
Affective disorder: depression	{ Endogenous depression	11	47.8	38.4	+19.9
	{ Reactive depression	5	39.0	29.8	+20.8
	{ Hysterical depression	6	37.3	37.5	-1.8
Constitutional schizophrenia	{ D.P. simplex	6	20.0	20.2	-1.5
	{ Catatonic schizophrenia	7	21.7	11.5	+18.5
	{ Hebephrenia	38	21.2	15.9	+10.5

* The regression equation used was: $\hat{X} = a$ plus bY , where $a = \bar{X} - \bar{b}Y$, and $b = r \frac{\sigma_X}{\sigma_Y} = \frac{\sum XY}{\sum Y^2}$.

(a) *Controls.*

Confirmation of Ray's (1946) findings is seen by the mean RT of 41.1 seconds (96.9 per cent. oxygen) for the present series of 112 normals; his series of 317 healthy young men yielded a mean of 37.7 seconds (95.9 per cent. oxygen). This concordance is important, since it indicates the change of site of examination from the back of the hand to the skin of the finger-nail fold makes no material difference. It probably indicates that such response is typical for capillaries in other regions of the body. The RT is similarly influenced by minimal breath-holding stress, a mean reduction of 17.7 per cent. comparing favourably with Ray's result of 20.4 per cent. The RT score shows that 71.4 per cent. of the present control group would be "physiologically efficient" according to Ray's criterion, although the mean RT score found here (+14.6) is considerably less than the +27.0 given by his group of highly trained pilots and riflemen during the war. It accords well, however, with one's clinical impression of the present series of controls. They included a high percentage of inductees, "depot men" and troops recently returned from overseas—by no means a highly selected "supernormal" group as was his, but a very much more representative sample of the average population. Oximetry with the Millikan instrument confirms these RT findings, an oxygen saturation of 92 per cent. or more being consistently found in all six healthy subjects studied by this alternative technique.

(b) *Neurotics.*

It is not so much in their RT values (mean 38.0 secs., 96.0 per cent. oxygen), which are somewhat lower than those of the controls, but in the RT score that the striking differentiation of this group from all others studied lies. The mean RT score of the neurotics is less than zero (−0.86) and, in fact, only 10.9 per cent. of these patients achieved an RT score of 10 or more. Re-examination of the clinical records of these few apparently misclassified "neurotic" subjects (they were all army personnel) revealed that at least

TABLE IV.—*Diagnostic Prediction Table: Showing Use of RT Test as a Means of Predicting the Diagnosis in Three Groups of Subjects.**

Predicted diagnosis on basis of RT and RT score.	Actual psychiatric diagnosis.			
	Controls.	Psycho- neurosis.	Constitutional schizophrenia.	Total.
Controls	99	13	0	112
Neurotics	14	46	4	64
Constitutional schizophrenia	0	0	47	47
Totals	113	59	51	223
Number correctly classified by test				192 out of 223.
Per cent. correctly classified				86.1 per cent.
Number incorrectly classified				31 out of 223.
i.e., per cent. misclassification				13.9 per cent.

* Results are based on scatterdiagram (Fig. B) using RT = 25 secs. and RT score + 5 as critical levels. The percentage misclassification of 13.9 is obviously highly significant.

two of them were near-defective, dull and backward individuals with a matrix intelligence rating of S.G. 5, while yet another two such Army patients, diagnosed as "chronic anxiety states," had histories of repeated attacks of depression and both had made serious attempts at suicide on more than one occasion. Including such patients as these and using an RT score of $+10$ or more as the critical break-point for normality, it can be seen that 82.8 per cent. of the neurotic group are correctly classified as neurotics, while 6.3 per cent. of them behaved physiologically in a similar fashion to the schizophrenic group.

(c) *Schizophrenics.*

(i) *Spectroscopic oximetry: British series.*

It became apparent early on while making these observations that the "constitutional," "nuclear" or "process" schizophrenic patient was behaving in a very different manner from the more psychogenically determined "paranoid" patient. If one groups the dementia praecox simplex, the catatonic schizophrenic and the hebephrenic into one "constitutional" group and the paranoid reaction type, the paranoid schizophrenic and the paraphrenic into a second, or "paranoid" group, then it can be seen (Figs. B and G) that no such constitutional schizophrenic in this present series of 51 cases had an RT which reached the critical level for normality of 25 seconds (92.1 per cent. oxygen)—the lowest figure ever reached by the individuals of the control group. Put in another way, this indicates that every one of these cases showed a well-marked peripheral capillary hypoxia of pathological degree. Breath-holding stress still further reduced the effective capillary oxygen content of these patients, giving an RT score within normal limits (plus 10.0).

As regards the second, or paranoid, group of schizophrenics, the data suggest that, from the point of view of capillary anoxia, this classification included at least two orders of disease process. Three cases would seem actually to have been examples of constitutional schizophrenia with an initial RT level of less than 25 seconds (92.1 per cent. oxygen), while another 5 of the total group of 16 came perilously near, or even below, this critical level under the influence of breath-holding stress.

(ii) *Discontinuous (RT) and continuous oximetry: American series.*

No differences were found to exist between the RT measurements of these two series of patients, the American schizophrenics falling into the same two physiological groupings of "constitutional" and "paranoid" schizophrenia. Oximetry by the Millikan technique showed that all patients had a blood oxygen saturation of less than 92 per cent., and it was even easy to correlate the blood oxygen saturation level with the degree of schizophreniform disintegration present, the two clinically least empathic cases reaching levels of 82 and 83 per cent. oxygen respectively. Table V gives the range of saturation levels for each patient, while Fig. F is an example of the fluctuations recorded during the hour's interview on one patient.

TABLE V.—Showing Ranges of Continuous (Photo-electric) and Discontinuous (Spectroscopic) Oximetry Reached during Psychiatric Interviews.—American Series.

Patient.	Age.	Diagnosis.	Range of per cent. O ₂ sat. (Millikan oximeter).	RT range (secs.).	RT with apnoeic stress (secs.).
1	37	Catatonic schizophrenia	91-92	22-24	18
2	24	Dementia praecox, simplex	87-88	9-21	15
3	29	"	91-93	23	16
4	24	Hebephrenia	86-90	18-23	19
5	23	"	84-87	8-15	—
6	25	"	90-91	18-22	—
7	26	"	82-85	5-6	—
8	27	"	89-91	15-24	17
9	31	"	87-88	13-20	11
10	29	Dementia praecox, simplex	87-90	20-27	24
11	41	Hebephrenia	90-92	19-25	18
12	55	Involutional depression	93-98	31-40	26
13	29	Paranoid schizophrenia	Refused	—	—
14	30	"	88-95	11-36	24
15	24	"	88-92	12-22	—
16	32	"	94-95	29-35	15
17	58	"	88-90	8-13	15
18	42	"	91-94	20-24	24
19	29	"	90-92	16-24	22
20	36	"	88-90	15-20	19

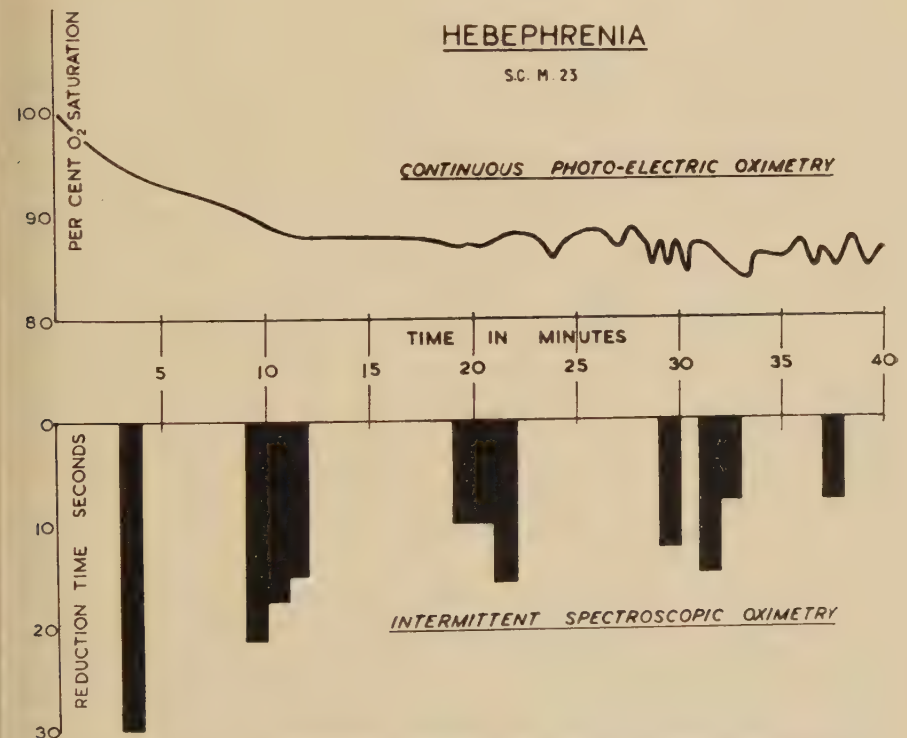


FIG. F.—Continuous photo-electric oximetry in a case of hebephrenia during a psychiatric interview. Oxygen inhalation through a B.L.B. mask was given for seven minutes prior to interview for standardization of the oximeter. Note fluctuations and baseline after effects of oxygen have worn off.—American series.

(d) *Affective Disorders.*

These form an interesting group of patients, for the standard deviations for this classification are the highest of all the diagnostic groups studied. This seems to be accounted for by the different subcategories of depression included. The single case of mania behaved as an example of endogenous depression, and together these 11 cases responded physiologically exactly as if they had belonged to the control group (mean RT = 47.8 seconds; 98.9 per cent. oxygen)—another illustration of the essential physiological normality of this class of patient, which has been repeatedly stressed in the literature. A rather less stable personality was found among the cases of the intermediate group of reactive depressions (mean RT = 39.0 seconds, 96.3 per cent. oxygen), while an entirely distinct physiological pattern was shown by the hysterical neurotic depressions. These patients, despite their clinical depression, none-the-less behaved in accordance with their underlying neurotic personality disorder and in a fashion similar to those of the psychoneurotic group proper (mean RT = 37.3; 95.8 per cent. oxygen; mean RT score = -1.8). Such differentiation would appear to be of major importance in determining the nature of treatment to be applied to such patients and the prognosis to be expected.

(e) *Response of Patients with Paranoid Schizophrenia and Depression to Stress.*

In addition to the differentiation of these two syndromes physiologically in terms of RT and RT score, it is interesting to detail the actual stress response of some of them in terms of capillary hypoxia. Nine (56.3 per cent.) of the 16 paranoid schizophrenics and 5 (31.3 per cent.) of the 16 endogenous and reactive depressives showed a borderline or pathological degree of capillary hypoxia when subjected to minimal breath-holding stress. This oximetric lability to voluntary apnoea is confirmed by the effects on these patients of various psychological stresses as seen in the interview situation. The introduction of affect-laden conflict material into the psychiatric interview caused a marked depression in the oxygen levels as determined by photo-electric oximetry, paranoid schizophrenic patients especially becoming rapidly anoxic under such stresses, and remaining so for the duration of the interview.

(f) *Psychopathic Personality.*

With a mean RT of 40.7 seconds (96.8 per cent. oxygen) and a mean RT score of plus 6.7, this group would appear to represent a low average normal range. Split up, however, into the two major subclassifications of psychopathy, it can be seen that the predominantly aggressive type is the more nearly normal from the point of view of the RT score (mean = plus 8.8), while the predominantly inadequate type was a borderline neurotic group with a normal RT (mean = 42.0 seconds, 97.2 per cent. oxygen) and a relatively low RT score (mean = +5.8).

(g) *Miscellaneous Organic Cases.*

The individual members of this small group had little in common save for the organic neurological history of their illnesses, yet physiologically they behaved in a homogeneous fashion. The RT values of most of the members of the group were in excess of those of the controls, some reaching levels as high as 78 and 93 seconds. Response to stress was often considerable, as can be seen from the high mean RT score of $+15.6$.

(h) *Use of the RT Investigation as a Prediction Test for Diagnosis.*

Fig. G shows how the values of RT plotted against RT score scatter with the three groups of controls, neurotics and constitutional schizophrenics. So

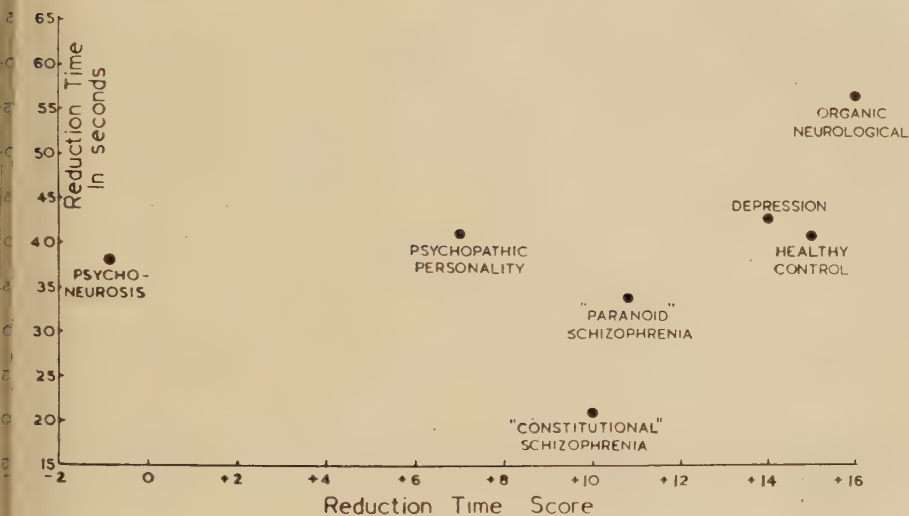


FIG. G.—Shows scatter of the means when the values for RT and RT score are plotted against each other for each of the seven major diagnostic groups studied.—English series.

far as the first and last groups are concerned, it can be seen that none of the controls has an RT value of less than 25 seconds and none of the schizophrenics attain that figure. Differentiation between these two groups is, therefore, possible with complete validity. When neurotics are compared with the controls, differentiation is not perfect but achieves a high degree. The prediction table (IV) has been prepared with the object of obtaining the greatest possible differentiation of the data, and it was found that this could be optimally achieved by shifting the critical RT score for normality to $+5$ or over, instead of the figure of $+10$ and over as suggested by Ray. The differential correlation for the three groups then becomes much greater, the misclassification for 223 individuals being 13.9 per cent. Since one would expect a number of potential neurotics in all normal populations of any magnitude (the "neurotic tenth"), the correlation coefficient is almost perfect.

DISCUSSION.

So far as the anoxaemia of constitutional schizophrenia is concerned, Hoskins' (1946) words are particularly apposite here. He remarks (p. 136): "As to how the lowering of the oxygen assimilation is brought about, more information is needed—and it is conceivable that an answer to this problem might actually reveal the essential mechanism of schizophrenia." Our present findings suggest that, in addition to Hoskins' report of a defective oxygen uptake in these cases, such anoxia may well be dependent upon disturbances at the capillary level of morphology and function. The capillary bed is the *effective* pathway of oxygen transport in the organism, since it is the means whereby oxygen first makes contact with the cardio-respiratory uptake mechanism, and it is probably the only route for its transfer to the cells of the central nervous system.

Now it is obvious that measurement of arterio-venous oxygen differences in blood taken from the internal jugular vein represents oxygen which has been in much closer relationship to the brain than any such estimation made on blood in peripheral vessels. Also obvious, however, is the fact that such determinations can only represent gross overall changes of oxygen saturation values and are subject to a large number of variables. The particular variables involved in the oximetric determination of peripheral capillary oxygen saturation are perhaps fewer; sources of technical error have been discussed by Elam *et al.* (1949), and physiologically they include the well-known tendency to peripheral arterial vasospasm in schizophrenics, acrocyanosis with local slowing of the circulation time and possibly differential capillary diffusion gradients. Peripheral vasoconstriction and acrocyanosis in schizophrenia have been recently studied especially in relation to catatonia (Shattock, 1950), and would appear to represent a homeostatic thermal regulating mechanism for purposes of conserving body heat.

In view of these factors therefore, and despite the fact that in normal control subjects there seems little doubt but that the results of spectroscopic and photo-electric oximetry are very highly correlated with alveolar oxygen tension and with arterial oxygen saturation levels, it cannot be maintained yet that such results are necessarily measures of cerebral capillary oxygen saturation in schizophrenic subjects, although the confirmatory work reported here showing concordance of the results of the two techniques must add considerable support to its probability. Granted the relationship, however, it would seem probable that the most likely explanation might be that the anoxaemia is the common end-result of a multitude of different causes. It is the probable aftermath of the head injuries (Shapiro, 1941), encephalitides (Kronfeld, 1940), intoxications (Schmidt, 1937), endocrinopathies (Schachter, 1937), rheumatic conditions (Bruetsch, 1940), as well as of the other conditions—including anoxic anoxia—already mentioned, and, as reactions to which, sometimes follows "schizophrenia," and it is the end-result also of a pathological process of environment acting on a predisposed constitution, for not everyone developing a similar degree of tissue anoxia develops automatically the reaction of schizophrenia.

SUMMARY.

(1) Spectroscopic oximetry was employed on 112 healthy controls and 183 psychiatric patients in a cross-sectional study and concurrent spectroscopic and photo-electric oximetry on an additional 26 subjects during a series of psychiatric interviews.

(2) By comparison with the healthy controls, all "constitutional" schizophrenic patients showed evidence of a significant degree of chronic anoxaemia. The factors of sex, age, duration of illness and subtype of symptomatology were shown to be relatively unimportant. "Paranoid" schizophrenic patients typically showed a low normal baseline level, but tended readily to become anoxaemic under the impact of various stresses.

(3) Neurotic patients differed from the controls in showing lower baseline levels and a "physiological efficiency" score comparable with that of physically ill patients. Endogenous forms of depression examined during and after physical treatment were found to resemble the control group in their responses, while neurotic forms of depression behaved like psychoneurotic patients in general. Cases of psychopathic personality, aggressive type, were essentially normal on test, but predominantly inadequate psychopaths tended toward neurotic scores. Organic neurological cases with psychiatric symptoms showed abnormally high values.

(4) An analysis of variance showed the above findings to be significant at the 1 per cent. level of confidence. Cross correlation of the results of the two oximetric techniques used in 285 simultaneous determinations yielded a coefficient of $+0.92$, and a convenient regression equation for the calculation of percentage arterial oxygen saturation from spectroscopic oximetry measurements.

(5) Oximetric methods were found to distinguish highly significantly between healthy controls, constitutional schizophrenics and neurotics, and their use in differential diagnosis, prediction and confirmation of psychiatric diagnosis is discussed.

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SYMPATHETIC BLOCKADE IN THE TREATMENT OF ANXIETY STATES.

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PATON and Zaimis (1949)¹ showed that the members of a series of compounds composed of two tri-methyl ammonium groups linked by a polymethylene chain had various actions, such as producing neuro-muscular blocking, inhibition of cholinesterase, a muscarine-like action and a blocking of impulses at the autonomic ganglia. It has been found that hexamethonium is the most active of the above compounds in these respects, and the autonomic ganglionic blocking properties have clinical applications. Hexamethonium is usually used clinically as a dibromide.

Considerable work has been done with the above compound in the treatment of hypertension of all types (Campbell and Robertson, 1950)².

The abolition of the secretion of hydrochloric acid after the drug has also led to its use in the treatment of peptic ulceration (Kay and Smith, 1950)³.

A consideration of the above pharmacological properties and indications for treatment has led to speculation with regard to any possible therapeutic value in the modification or elimination of the somatic manifestations of anxiety states. The use of hexamethonium in this way was, of course, considered as an adjuvant to psychotherapy, and in no sense a substitute for it. It was, however, believed that if some of the more overt somatic symptoms and signs, associated with anxiety states could be resolved, part of the vicious cycle could be broken, and the patient better prepared for and indeed more accessible to orthodox psychotherapeutic procedures.

The work of Cannon (1935)⁴ has emphasized that in some emotional states the sympathetic nervous system is stimulated, as shown by tachycardia, rise of blood-pressure due to vasoconstriction, dilatation of the pupil, erection of hairs, mobilization of liver glycogen, and sweating. He also showed that in these states there was a discharge of adrenaline from the adrenal medulla, and that the adrenaline so secreted reinforced the actions produced directly by the sympathetic nerves. It is of course true that all emotional exteriorization is not equivalent to sympathetic stimulation. Parasympathetic overactivity also predominates in some emotional states, and the work of Wolf and Wolff (1943)⁵ demonstrates very strikingly how, in the case of the stomach, emotional states may produce either sympathetic or parasympathetic overactivity.

A hypothesis such as the James-Lange theory of emotions^{6, 7} which declared in essence that the sensations of visceral and vasomotor changes were the emotions, is no longer acceptable to-day. It is, however, the aim of this paper to suggest that the bodily accompaniments of emotion, particularly those accompanying anxiety, play an important part in the vicious body-mind

cycle in some cases of psychoneurotic syndromes, and that, if by chemical means the somatic and visceral manifestations can be lessened, the patient is in a much better state to benefit from ordinary psychotherapy.

The material considered was a group of 17 patients, 12 females and 5 males, whose main symptomatology was a combination of psychological components of anxiety and tension, and somatic manifestations such as sweating, tremor, palpitations, etc. All these patients had received courses of various psychotherapeutic procedures before commencing treatment. Their response to hexamethonium was tabulated by the effect of the drug on the different sympatheticotonic symptoms and signs. Four of the above group received the treatment whilst in hospital; the remainder were treated as out-patients attending a psychiatric clinic at a general hospital.

The accompanying table summarizes the case material, dosage and duration of treatment by the drug, and the results obtained.

DOSAGE AND DURATION OF TREATMENT.

As the majority of the patients were treated on an out-patient basis, great care was exercised in gradually increasing the dose. Each patient took one tablet (0.25 gm.) after meals twice a day for five days; then three times a day for another five days; and so on up to four or five tablets every day. It was found that the best objective results were obtained between the sixth and tenth weeks of such treatment, although, as the table shows, there were several deviations from this. Since it has been repeatedly shown that excretion may be delayed and action of the drug prolonged in cases of renal failure, any patient with a history of renal dysfunction was excluded and a routine urine examination was carried out in each case. A history of a cerebral or coronary vascular incident was also considered a contra-indication to treatment.

Lowering of blood pressure—the usual clinical reason for the exhibition of hexamethonium—was seen in eleven of the above cases, and the reduction averaged between 5 and 10 mm. (systolic and diastolic). It is felt that in the small dosage as above, used with adequate spacing of the various increases of dosage, the alarming sequelae which sometimes follow a sudden reduction of a high blood pressure were not seen. In only Case 13 was the blood pressure consistently high, 160/105, and at the end of the treatment this had fallen to 140/90. The full extent of this fall was not, however, seen until about the eighth week of treatment.

TOXIC EFFECTS.

Three patients initially complained of anorexia, presumably due to the suppression of hydrochloric acid secretion. This symptom soon disappeared and it was essentially of a minor character. Another patient complained of blurring of vision, which came on during the third week of treatment, but lasted only a couple of days. It is known that the drug can cause partial paralysis of accommodation. Approximately half the patients complained of nausea during the second week, but this was never really disturbing, and in no case was it necessary to stop or reduce the administration of the drug.

DISCUSSION.

Many observers, including Wittkower (1935),⁸ have discussed the many physical syndromes, signs and symptoms found both clinically and experimentally as sequelae to emotional stimuli. It is also well known clinically that different subjects show very strikingly the same somatic manifestations to different emotional states, and, whilst from patient to patient different components are emphasized, there is often a specific effect in any given individual. Thus, one person may habitually respond to emotional upset by headaches, probably due to local vasodilation, another by sweating or tremulousness, and yet another by palpitations (tachycardia). All these may occur alone or in various combinations.

The above series of patients, by no means a common group, in a large series of states of anxiety as seen in either hospital or out-patient clinics, were chosen because of marked physiological somatic manifestations, and because many of them had, as their main complaint, these very components. Thus, many patients actually complained of sweating and tremors, and, as can be seen from the table, most of the patients had these signs. Such objective evidence was of course valuable in the assessment of results.

Sometimes somatic features, e.g., sweating (as in Case 1) represented the main factor disturbing the patient, and became so prominent that projection ultimately gave rise to the sequelae of ideas of reference—i.e., “people talk about the way I smell.” The excellent result of sympathetic blockade in this case completely relieved the sweating with rapid disappearance of the ideas of reference, and, for the first time, made the patient suitable for investigation and exploration in the search for his basic causes of anxiety.

In many cases psychological states of tension were relieved by a resolution of somatic symptoms and signs which had for long caused the patients alarm because of their possible malignant significance, e.g., attacks of palpitations, which were always associated with, in their minds, heart disease. The drug is also invaluable in such cases, after cessation of the attacks of tachycardia, in demonstrating to the patient the physiological significance of such states.

CONCLUSIONS.

The results obtained suggest that hexamethonium is an effective adjuvant in the treatment of anxiety states. The most satisfactory results are seen in patients who have marked physiological reactions, e.g., sweating and tremulousness, to anxiety. Definite and in some cases equally marked beneficial results are obtained in subjective reactions, e.g. palpitations. In some cases of marked sweating due to anxiety, which is causing considerable distress, hexamethonium can be expected to produce almost complete relief of the sweating and the associated psychological tension. It is, however, emphasized that this drug, as used in this manner, is in no case a substitute for orthodox psychological exploration and therapy. It is, however, submitted that in cases hitherto resistant to such treatment it may have an excellent adjuvant value in the specific group of cases here under discussion. The ease of adminis-

Case.	Age and sex.	Diagnosis.	Previous treatment.	Hexa-methonium (gm./day).	Duration of treatment.	Objective improvement.			Subjective improvement.	
						Tremor.	Lowering of B.P.	Sweating.	Palpitations.	Tension.
1	28 (M)	Chronic anxiety state, with main complaint of excessive sweating	Six months' psychotherapy accompanied by sedatives	1.25	12 weeks	+	+	++	+	++
2	44 (F)	Reactive anxiety with marked tremulousness	Three months' psychotherapy together with sedatives	1.0	5 "	+++	-	+	-	+
3	43 (F)	Chronic anxiety state of almost 4 years' duration. Marked states of panic with sweating, palpitation and tremor	Psychotherapy for two years, including four months in a neurosis centre	1.25	7 "	++	+	++	++	++
4	40 (M)	Chronic anxiety state with main complaint of palpitation	Psychotherapy for nearly nine months	1.0	8 "	-	+	+	+	-
5	60 (M)	Chronic anxiety state with associated depression. Generalized tremor marked feature.	Sedation and five months in a mental hospital	1.25	9 "	++	+	+-	+	+
6	54 (F)	Reactive anxiety with hypochondriasis. Much tremulousness	Sedation and psychotherapy	1.0	8 "	+++	+	-	++	+
7	38 (M)	Chronic anxiety state with marked attacks of panic; characterized by palpitation, sweating, and tremulousness	Psychotherapy at varied intervals for almost 4 years	1.25	10 "	+++	+	++	++	++
8	37 (F)	Acute anxiety state with marked attacks of panic, characterized by palpitation, sweating and tremulousness	Psychotherapy for one month together with sedatives	1.25	4 "	+++	+	++	+	++
9	48 (F)	Recurrent depression with associated anxiety state	Electroplexy on two occasions (six shocks in each course). Psychotherapy; sedatives	1.0	8 "	+	-	-	++	++

Case.	Age and Sex.	Diagnosis.	Previous treatment.	Hexamethonium (gm./day).	Duration of treatment.	Objective improvement.			Subjective improvement.	
						Tremor.	Lowering of B.P.	Sweating.	Palpitations.	Tension.
10	59 (F)	Chronic anxiety state with marked sweating. An associated seborrhoeic dermatitis	Psychotherapy for 8 months	1.25	10	+	-	+	-	+
11	28 (F)	Chronic anxiety state with marked tremulousness and agitation	Psychotherapy for 9 months accompanied by sedatives	1.0	12	+	+	+	+	-
12	39 (F)	Agitated depression with associated anxiety features, particularly of sweating	Electroplexy (6 shocks) four months before. Psychotherapy	1.25	8	+	+	+	-	-
13	45 (F)	Anxiety hysteria with marked tremor, sweating and palpitations	Psychotherapy and sedation for nearly one year	1.0	10	+	+	+	+	+
14	40 (M)	Chronic anxiety state with marked tremor and palpitations	Psychotherapy and treatment in a mental hospital for 8 months	1.25	6	+	+	+	+	-
15	26 (F)	Chronic anxiety state with marked tremor and sweating	Psychotherapy and sedatives for 3 months	1.0	7	+	+	+	+	+
16	33 (F)	Recurrent depression, with associated anxiety	Electroplexy on three occasions relieving the depression but leaving always anxiety with associated tremulousness	1.25	6	+	+	+	-	+
17	39 (F)	Reactive anxiety with marked tremulousness and sweating	Psychotherapy with "stimulants" for nearly five months	1.25	8	+	+	+	+	+

+ = Degree of improvement.

tration and the unlikelihood of serious toxic reactions with the dosage used would seem to warrant further trial and elucidation in the treatment of such cases.

SUMMARY.

1. 17 patients (12 female and 5 male) with anxiety states of various types were treated with hexamethonium, in a dosage of 1 to 1.25 gm./day by mouth, for periods of 6 to 15 weeks.

2. The cases selected all showed marked physiological somatic manifestations to anxiety.

3. Varying degrees of improvement were shown in all the patients and in some, excellent results, by removing physiological disturbances, which in their turn were causing the patients much anxiety.

4. Subsequent to the use of the drug most patients were far more accessible to ordinary psychotherapeutic measures than before.

5. Toxic effects were few and of relatively little importance.

6. It is concluded that in the special group of patients showing these features of sympathetic overactivity, hexamethonium is a very useful adjuvant to psychotherapy.

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THE EFFECTS OF ETHYL ALCOHOL AND ACETALDEHYDE ON MAZE BEHAVIOUR AND MOTOR CO-ORDINATION IN RATS.

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THE study of moderate degrees of alcoholic intoxication in such an animal as the rat demands methods of assessment of the state of the animals, which is a requirement not easy to provide. So far as the more complex integrated activity of the central nervous system is concerned, the use of a suitable maze affords some information of an objective kind. The book by Warden and others (1935) gives much information about construction and operation of mazes. Methods of recording based on projection by a lens (Yerkes and Kellog 1914; Watson, 1914) and the use of electrical contacts (Tolman and Jeffress 1925; Heron, 1933) have been described for rat mazes, while Miles (1928) has suggested the use of blotting-paper in conjunction with an ink writer to show relative speeds within a maze.

Modification of maze behaviour, produced by administration of alcohol, has been described by Varner (1933), and Miller and Miles (1936), but no attempt seems to have been made to employ the maze as a tool in studying the intoxication process. In the work described in this paper the aim has been to establish for the rats used the kind of alteration of maze behaviour produced by alcohol administration, employing for the purposes a simple and novel form of recording mechanism. A test for motor co-ordination has been used for comparison purposes to show the state of the lower nerve centres, and the modification of the alcoholic intoxication process produced by acetaldehyde has been studied.

METHODS.

Rat behaviour was studied in a plane four feet square maze of the Carr pattern (1917), constructed of aluminium, with perspex covering. A starting box was fitted at the entry to the maze, with a gate, controlled by the operator, which prevented re-entry to the box. No provision was made to prevent retracing in the runs, which were 4 inches wide divided by partitions 4 inches high.

The apparatus employed to record the rats' performance is illustrated diagrammatically in Fig. 1. The geometrical principle involved, which is applicable to plane mazes of any form, can be explained most simply as follows. If the eye is placed at *o*, straight lines drawn from *o* to the top of the maze walls and partitions intersect the horizontal sheet of perspex *pq* in a figure which is a replica of the maze, reduced in the ratio *op/om*. The pantograph arrangement shown in the plan still further reduces this figure in the ratio

ST/SR, and by means of the ink writer W, the path of a rat round the maze is reproduced on paper on a fixed scale of reduction, provided that F is kept in the line joining O to the rat. The maze is conveniently placed just above floor level.

The most effective type of sight was found to be a small strip of perspex fastened to the pantograph arm at F, bent in such a way as to rest on the perspex sheet PQ (with a small piece of leatherette interposed), and pierced with a hole for the tip of the index finger, the latter being moved to follow behind the rat. An alternative form of sight with crosswires was found useful in preparing the reduced plan of the maze on paper for transfer to a stencil. The extensions of the sight and writer beyond the major and minor arms of the pantograph

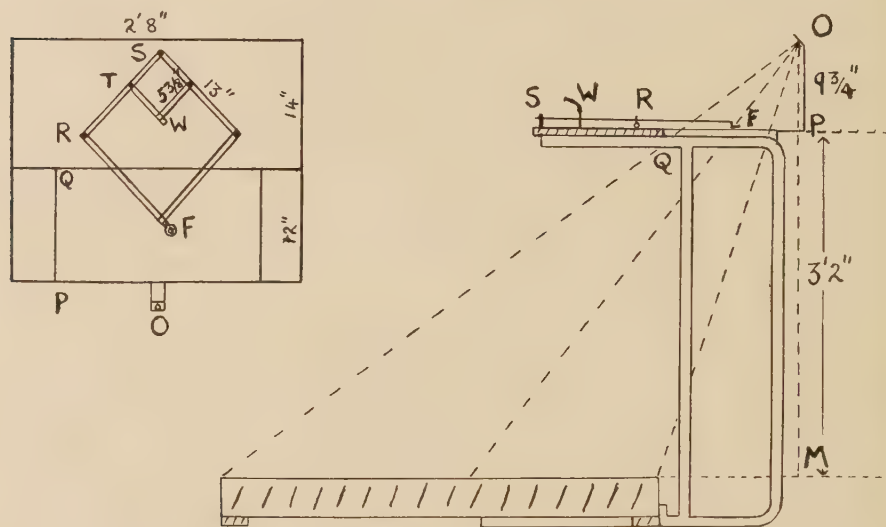


FIG. 1.—Diagram of maze recording apparatus. For description of parts refer to text.

respectively must of course be in the ratio of the arms, and the accuracy can be checked by observing that F, W and S remain in a straight line for all positions of the pantograph. It can be readily shown that the scale of reproduction is unaffected by the prolongation of the arms in this way.

The tracings were recorded on stencilled impressions of the maze plan, made on octavo size paper, with a scale marked along one side to facilitate measurement of maze tracks with a map measurer if desired. The scale of final reproduction was 1 : 12. The papers were provided with two guide lines at right angles to locate the perforations, made with a double paper punch, which matched positioning studs on the pantograph table. Those perforations were also used for filing purposes. A movable spring clip held the paper flat. Spaces were provided for entering the animal's number, the date, number of run, time taken by stopwatch for the run, and distance travelled in the maze. Other information could be written in by the operator, who thus had in compact form all relevant information about any particular run. The necessity for

some form of semi-automatic recording became obvious when it was found that highly-trained rats could run the entire maze (of minimal distance 27 feet) in 9-15 seconds.

For study of the motor co-ordination, the grid test already described by one of us (1948) was used. An adult rat (180-200 gm.) when placed head downwards on a wire grid of half-inch mesh held vertically, normally turns smartly on its hindquarters and climbs up. Should the co-ordination of the hind limbs and toes be affected, as happens at a very early stage in alcohol intoxication, the rat fails to perform the movement adequately, and the hindquarters slither down out of control. At a later stage of intoxication control of the forelegs may be also impaired, and the rat will then be incapable of holding on to the grid. For convenience, the various stages were represented as follows:

-ve, motor co-ordination unaffected. +ve, hindquarters slithering, but rat capable of maintaining its hold with front paws. ++ as +, but losing grip with front paws. +++ , rat falling off grid when first put on, with corneal reflex still present. ++++ , rat judged unconscious (corneal reflex absent).

RESULTS.

Albino Wistar rats of weight 160-200 gm. and of both sexes were first of all trained to a high uniform level of performance in the maze. Milk was used in the end compartment as incentive, the rats being deprived of water overnight. In some experiments food was allowed, in others this also was withdrawn. A uniform procedure was established after training, in which the rats were allowed three runs in the maze daily at fixed times. One day of rest was allowed between each experiment.

Training occupied 2-3 weeks, at the end of which time errors were practically completely eliminated. The disturbances of maze behaviour observed in such fully trained animals after administration of alcohol by stomach-tube were of two kinds: (a) refusal to run the maze, and (b) wrong entries and eventual stoppage in a cul-de-sac, or return to the starting position. Those were the forms of behaviour most commonly encountered when alcohol was producing a marked disturbance, though occasionally completion of the maze with errors (wrong entries and retracing) was observed. When a rat did not succeed in completing the maze in $2\frac{1}{2}$ minutes, failure was recorded. It is perhaps worth comment, although systematic work on this point was not carried out, that at an early stage in training a comparatively small dose of alcohol (1.0-1.5 ml. 30 per cent. alcohol for 160 gm. rat) was observed to produce very marked disturbance in rats which were beginning to perform well. For this reason it was considered likely that the maze behaviour might prove more sensitive, as an indication of the disturbances produced by alcohol, than the hind limb co-ordination test. When, however, the maze performance was fully established, considerably higher doses of alcohol were required to modify it. As will be seen presently, it is not possible to make a generally valid statement regarding the relative sensitivity to alcohol of the maze behaviour and hind limb co-ordination.

During the course of experiments carried out with alcohol it was frequently observed that the degree of inco-ordination of the hind limbs appeared to bear no relation to the extent of disturbance of maze behaviour. Thus in extreme cases, rats have been seen to make a faultless passage of the maze at greatly reduced speed (1-1½ minutes) whilst staggering and hardly able to walk. In other less frequent cases, rats have failed to find their way, although the signs of motor inco-ordination were absent. Such observations would lead one to postulate that disturbances of the more highly integrated forms of nervous activity produced by alcohol can occur independently of those involving lower levels. This possibility had been previously foreseen, though not experimentally realized in another connection (MacLeod, 1948). It is also in accordance with everyday observation of the behaviour of drunken human subjects.

The general features of maze behaviour in groups of rats before and after treatment with alcohol (4 ml. 30 per cent. alcohol for 160 gm. rat) are shown in Table I.

TABLE I.—*Maze Behaviour of Rats Before and After Alcohol Administration.*

Type of behaviour.	Males.		Females.	
	Before alcohol.	After alcohol.	Before alcohol.	After alcohol.
No false entry . . .	64	68	69	63
1 ditto . . .	41	6	21	12
2 „ . . .	6	5	16	6
3 „ . . .	3	1	5	0
4 „ . . .	0	0	3	0
Failure to complete the maze . . .	0	34	0	33

The figures show the number of runs falling within each category. 19 male and 19 female rats made 6 runs each. The dose of alcohol was 4 ml. 30 per cent. alcohol for 160 gm. rat.

It will be seen that in the groups the effect of alcohol is to diminish the frequency of small errors, whilst causing the appearance of a moderately high proportion of failures to complete the maze. The proportion of error-free runs was unaffected—a fact which suggests that the tendency to commit small errors is exaggerated by alcohol. This conclusion, it must be emphasized, applies to the group as a whole, not to individual rats.

With such information on the disturbing effect of alcohol it was possible to plan further experiments, using the fully-trained rats available. For reasons which will be mentioned in the discussion, it was of particular interest to study the effects of acetaldehyde upon alcohol intoxication. Acetaldehyde itself is capable of producing in rats an intoxication of short duration (Stotz, Westersfeld and Berg, 1943). A new series of observations was undertaken, in which the effects of alcohol, acetaldehyde and alcohol with acetaldehyde were investigated, at intervals of ¼ hour, ½ hour and ¾ hour after administration in each case. It was necessary to spread those experiments over an interval of days, and comparisons were made between corresponding runs, the programme being arranged on a strict time basis to facilitate comparison. The standard dose of alcohol was as before, 4 ml. 30 per cent. alcohol for 160 gm. rat, and for

acetaldehyde, 4 ml. 5 per cent. solution (made from freshly distilled acetaldehyde), administration being by stomach-tube in both cases. The results are shown in Table II, from which it appears that when both alcohol and acetaldehyde were administered, the disturbance of maze behaviour was much more

TABLE II.—*Maze Behaviour and Motor Co-ordination of Rats after Administration of Alcohol and Acetaldehyde.*

Run No.	Alcohol.			Alcohol and acetaldehyde.			Acetaldehyde.		
	1.	2.	3.	1.	2.	3.	1.	2.	3.
No false entry	17	16	16	3	5	7	5	15	14
1 ditto	1	2	1	3	0	0	5	2	4
2 „	1	1	0	0	0	0	1	0	1
3 „	0	0	0	0	0	0	1	0	0
Failure to run maze	7	7	9	20	21	19	14	9	7
Grid test — ve	3	3	2	0	1	1	18	22	24
+ ve	21	22	24	14	11	10	8	4	2
++	2	1	0	6	3	2	0	0	0
+++	0	0	0	4	6	7	0	0	0
++++	0	0	0	2	5	6	0	0	0

The numbers in the columns show the number of maze runs coming within each category. 26 rats were used, 12 females and 14 males. The dose of alcohol was 4 ml. 30 per cent. alcohol, and of acetaldehyde 4 ml. 5 per cent. (freshly distilled) for 160 gm. rat. In combination, 4 ml. were used containing the requisite amounts of alcohol and acetaldehyde.

marked in the second and third runs than was the case with alcohol and acetaldehyde separately. In considering the data it must be borne in mind that the effect produced by acetaldehyde alone is of short duration. This is well seen in comparing the results obtained one quarter of an hour after administration of acetaldehyde, with those corresponding to longer intervals. A similar general tendency appears in the records of performance on the grid.

DISCUSSION.

In the past much attention has been devoted to the subject of the metabolism of alcohol, particularly its rate of metabolism as indicated by blood alcohol curves. Such studies, whilst fruitful enough in certain directions, do not enlighten us regarding the manner in which alcohol produces its intoxicating effects upon the central nervous system, but deal rather with the factors affecting the duration of such intoxication. The view commonly accepted by the majority of workers (Eggleton, 1940; Lundsgaard, 1937) is that disposal of alcohol is effected principally by the liver, though some (*cf.* Dewan, 1943) have maintained that appreciable oxidation can occur in the brain.

The study of alcohol intoxication as a functional disturbance related to blood-alcohol levels has been undertaken in human subjects (Newman and Abramson, 1941; Eggleton, 1941), and some important conclusions have been drawn regarding the adaptation of the central nervous system to alcohol. Experiments upon humans, however, must inevitably involve serious limitations in design. The line of approach recorded in the present paper and elsewhere (MacLeod, 1948), whilst certainly not providing a final solution, may serve to

indicate the manner in which one may overcome some of the difficulties connected with the use of laboratory animals in studies of the alcoholic intoxication process, occurring in the functioning nervous system of vertebrates.

Attention has been drawn to the relationship of acetaldehyde to alcohol intoxication by reports of the efficacy of the substance tetraethylthiuramdisulphide ("Antabuse") (Hald and Jacobsen, 1948; O. Martensen-Larsen, 1948) in the treatment of alcoholism. This substance has been shown to cause an increased level of acetaldehyde in the blood following ingestion of alcohol. The question may naturally be asked, how far the presence of acetaldehyde following ingestion of alcohol under normal circumstances, which was demonstrated by Stotz (1943), can account for the signs of alcohol intoxication. Published data of one of us (MacLeod, 1950) in repetition of Stotz's work have shown that the levels of acetaldehyde attained in the blood of rats following administration of alcohol are insufficient by themselves to account for the degree of intoxication observed.

It appears, however, from the experiments recorded in this paper that one cannot readily exclude the possibility that acetaldehyde in the presence of alcohol may account for some exacerbation of the intoxication, that there is, in fact some kind of synergism, broadly speaking, between these substances. The mechanism of action of acetaldehyde is no more understood in detail than is that of alcohol. On the basis of our own observations, in the series of experiments here described and others of a similar character, the following features of the acetaldehyde intoxication may be added to those described by Stotz *et al.* (1943). Doses of acetaldehyde sufficient to produce unconsciousness have also invariably produced very marked retardation of the heart-beat in rats, recovery of the heart preceding return of consciousness. In cases where death has followed administration of acetaldehyde it has been frequently noticed that the brains of the animals were very markedly anaemic, whilst there was marked capillary congestion throughout the entire splanchnic area. These findings would suggest that a cardio-vascular disturbance might account for the apparent intoxicating effects of acetaldehyde.

On the other hand, in cases where acetaldehyde and alcohol have been administered simultaneously, the apparent synergistic effects already noted have persisted long after the passing of the initial cardiac disturbance, and also long after the usual period of recovery from acetaldehyde, when given by itself (10-15 minutes). It is not unthinkable that the disposal of acetaldehyde may be hampered in the presence of alcohol. Though present indications render this explanation somewhat unlikely, further work will be needed to elucidate this point, as well as to decide whether the action of acetaldehyde on the nervous system is secondary to vascular disturbance, or the latter secondary to a direct action on nervous centres including the medulla oblongata. Evidence is not lacking that acetaldehyde in physiologically tolerable concentrations can enter into enzymic reactions of known types (Stotz *et al.*, 1943; Racker, 1949) and should it appear that its so-called intoxicating action is related to its behaviour in such systems, this substance might be a valuable tool in the elucidation of the biochemical disturbances involved in intoxication by ethyl alcohol.

SUMMARY.

1. A method of semi-automatic recording applicable to plane mazes is described.

2. The effects of ethyl alcohol in modifying behaviour of rats in a Carr square maze are described in conjunction with a simple test for muscular inco-ordination.

3. Attention is drawn to the apparent synergistic action of ethyl alcohol and acetaldehyde in the production of signs of intoxication.

Our thanks are due to Professor F. L. Golla for constant advice and encouragement during the course of the work. Mr. H. Pask and Mr. D. Roberts gave most valuable help in constructing the maze and recording apparatus. The Monthly Bulletin Research Fund of the British Society for the Study of Addiction has given generous support throughout.

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THE USE OF COLOUR IN THE PAINTINGS OF PSYCHOTICS.

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INTRODUCTION.

STUDENTS of the paintings produced by mental hospital patients believe that schizophrenics show peculiarities in their use of colour. Impressions in the matter have been summarized by Reitman (1950). Schizophrenics, especially the chronic, seem to favour colours avoided by others, particularly shades of mauvish-red. They put colours into relationships that others find displeasing. They employ colours more boldly than others. Sometimes, it would appear, they purposely depict objects in colours at variance with those possessed in real perception.

Such impressions have not yet been quantitatively verified or experimentally elucidated. The following enquiry was pursued to throw more light on the question by—

- (a) counting the frequencies with which colours were employed in the paintings of mental hospital patients of various classes ;
- (b) counting the frequencies with which displeasing combinations, bold colours, unrealistic colours and the like occurred in such paintings ;
- (c) contrasting the choices of schizophrenics, non-schizophrenic patients and normal individuals in colouring a picture where shapes were already drawn in outline ;
- (d) comparing the same patients as to their liking for realistic and unrealistic colourings in drawings shown to them ;
- (e) comparing them as to their liking for isolated colours painted on cards ;
- (f) comparing them as to their liking for combinations of colours ;
- (g) comparing them as to the strength of feeling roused in them by colours ;
- (h) investigating differences amongst them in the associations that they connected with particular colours.

FREQUENCIES OF COLOURS IN PAINTINGS.

The paintings examined were those carried out in art-groups by 689 in-patients of Netherne Hospital between October, 1946, and December, 1950. The primary aim was to contrast the work of schizophrenics and non-schizophrenics. "Schizophrenics" were taken to include all definitely diagnosed as such or as paraphrenics. "Non-schizophrenics" were taken to include all definitely diagnosed as depressives, psychopaths or psychoneurotics. Manics,

epileptics, miscellaneous organics and patients in whom a schizophrenic reactivity was suspected but not demonstrated were excluded from consideration. The work of patients that had produced fewer than ten paintings was also ignored, because their opportunity to display their use of colour seemed inadequate. These exclusions reduced the number of patients actually considered to 176.

A distinction between the work of chronic and that of recent patients was imposed by the way in which the paintings had been collected. Here, "chronic" applies to patients who had been in hospital a long time, usually in closed wards, and whose recovery or readjustment was unlikely, "recent" applies to patients in reception wards or convalescent villas. Chronic and recent patients had never been mixed in an art-group but had always painted in different studios. In other respects the conditions under which they had painted had been the same. The chronic patients were all females, the recent of both sexes. Thus the contrast schizophrenic versus non-schizophrenic could be made within three classes: chronic females, recent females and recent males. Further contrasts were possible, within the schizophrenic and non-schizophrenic classes, between chronic and recent females for differences due to chronicity and between recent females and males for differences due to sex.

Consideration was given to the frequencies with which the following colours were employed: red, yellow, green, blue, purple, mauve, black, brown, grey and white. The colour-names were taken in a broad classificatory sense. Shades, tints and intermediate colours were classed according to their predominant appearance, except in the case of the blue-red series. Here "purple" was applied to blues with a definite component of red and "mauve" to reds with a definite component of blue. Where an area of paper was left unpainted with the obvious intention of representing white it was counted as the use of white. The occurrence of a colour in a given painting was weighted according to the amount of its employment: one point where it was used in a minor or subordinate way, two points where it had an extensive or important rôle, three points where it emphatically dominated all or nearly all the other colours in the painting. The number of paintings per patient showed an extreme variation. To make conditions of practice and self-confidence as similar as possible for all, the occurrence of colours was counted only in a patient's first ten paintings. The weighted frequency of each colour in each patient was thus expressed as an integer in the range 0 to 30. The counting and weighting were carried out in ignorance of diagnoses so far as the great majority of cases was concerned. The mean weighted frequencies of the various classes for each colour are shown in Table I. Statistically significant differences between class-means, tested by Student's *t*-ratio, are shown in Table II.

Differences between schizophrenics and non-schizophrenics are relatively trivial; those between chronic and recent patients are striking, especially within the schizophrenic class. Chronics show a more extensive use of purple and mauve and a less extensive use of grey. Among the schizophrenics, recent males are nearer than the recent females to the chronic females in their use of purple and mauve; evidence from the case-histories suggested that

TABLE I.—*Paintings : Mean Weighted Frequencies of Colours.*

Colours.	Schizophrenics.			Non-schizophrenics.		
	Chronic females.	Recent females.	Recent males.	Chronic females.	Recent females.	Recent males.
Red . . .	8.40	8.78	11.04	9.93	9.95	8.82
Yellow . . .	10.94	10.67	11.19	13.67	10.40	11.00
Green . . .	17.06	15.72	15.33	15.53	14.10	18.00
Blue . . .	10.86	11.55	12.38	11.53	13.45	10.73
Purple . . .	8.91	4.49	6.79	7.20	4.90	5.27
Mauve . . .	9.31	5.82	6.88	6.80	6.55	5.36
Black . . .	5.26	6.02	6.33	4.20	7.55	6.64
Brown . . .	11.80	10.63	10.75	11.93	8.68	9.36
Grey . . .	3.26	6.06	5.96	3.27	6.15	9.36
White . . .	4.97	5.49	4.60	6.53	5.60	6.73
No. of cases . . .	35	51	24	15	40	11

TABLE II.—*Colour in Paintings : Statistically Significant Differences.*

Colours.	Significantly more abundant in	t.	df.	p.
Red . . .	Male than female recent schizophrenics . . .	2.808	73	< .01
Yellow . . .	Chronic than recent non-schizophrenic females . . .	2.804	53	< .01
Green . . .	Male than female recent non-schizophrenics . . .	2.228	49	< .05
Blue . . .	— . . .	—	—	—
Purple . . .	Chronic than recent schizophrenic females . . .	4.146	84	< .01
„ . . .	Chronic than recent non-schizophrenic females . . .	2.137	53	< .05
„ . . .	Male than female recent schizophrenics . . .	2.087	73	< .05
Mauve . . .	Chronic than recent schizophrenic females . . .	3.629	84	< .01
Black . . .	— . . .	—	—	—
Brown . . .	— . . .	—	—	—
Grey . . .	Non-schizophrenic than schizophrenic recent males . . .	2.061	33	< .05
„ . . .	Recent than chronic schizophrenic females . . .	3.334	84	< .01
„ . . .	Recent than chronic non-schizophrenic females . . .	2.482	53	< .05
„ . . .	Male than female recent non-schizophrenics . . .	2.026	49	< .05
White . . .	— . . .	—	—	—

seriously ill patients were proportionately more numerous among the males. Differences in regard to red, yellow and green probably depend only on sampling fluctuations. The abundance of green in all classes and the employment of brown beyond what might be expected arise because landscapes were the most frequently depicted subject-matter.

OTHER ASPECTS OF COLOUR IN PAINTINGS.

A count was made of the frequency with which the following occurred in the first ten paintings of each patient :

(a) *Bright* paintings, where strikingly brilliant or highly saturated colours were used ;

(b) *dull* paintings, where a sombre effect was produced by a dominance of black, brown and grey, or the shading of other colours with them ;

(c) *Pale* paintings, where the pigments were greatly diluted with water ;

(d) *heavy* paintings, where the paint was laid very thickly on the paper ;

(e) paintings with *unrealistic colours*, showing for example green hair or blue faces ;

(f) paintings with *displeasing colour-combinations*, realistic or unrealistic, for instance that of a cat with a white face, a purple, mauve and green body, green and brown legs, and a bright red tail ;

(g) paintings with *patterned colours*, arranged in some aesthetic order transcending pure representation.

As four of these modes of using colour occurred with zero frequency in an absolute majority of patients, it was convenient to treat them all in terms of absence or presence. Table III shows the numbers in the various classes that displayed each mode. The statistical significance of differences was tested by the exact binomial-product method (Fisher, 1950).

TABLE III.—*Paintings : Modes of Using Colour.*

	Schizophrenics.			Non-schizophrenics.		
	Chronic females.	Recent females.	Recent males.	Chronic females.	Recent females.	Recent males.
No. of cases	35	51	24	15	40	11
No. showing—						
1. <i>Bright</i> paintings	18	29	16	11	19	4
2. <i>Dull</i> paintings	6	17	8	3	10	4
3. <i>Pale</i> paintings	10	24	9	7	18	3
4. <i>Heavy</i> paintings	27	27	15	10	17	5
5. <i>Unrealistic</i> colours	11	9	7	2	5	1
6. <i>Displeasing</i> colour combinations	24	19	12	8	16	5
7. <i>Patterned</i> colours	25	35	18	11	25	9

Statistically significant differences are confined to the comparison chronic versus recent female schizophrenics. The chronics have significantly fewer dull ($p=0.051$) and pale ($p=0.041$) paintings, and very significantly more heavy paintings ($p=0.014$) and displeasing colour-combinations ($p=0.005$). In these comparisons the use of unrealistic colours is commoner among schizophrenics but the difference is not statistically significant. If the total schizophrenics, however, are compared with the total non-schizophrenics there is a statistically significant difference ($p=0.021$).

COLOURING A DRAWING.

In the experimental parts of the investigation, conducted simultaneously with the foregoing counts, 36 schizophrenics were contrasted with 36 non-schizophrenics (depressives and psycho-neurotics), all female chronic in-patients of Netherne Hospital. Both samples were contrasted with eighteen student nurses as normal controls. The chronic patients were distinct from those whose paintings have just been considered. The schizophrenics in the experimental sample were closely similar in degree of illness to the chronic schizophrenic painters but, inadvertently, the non-schizophrenics were for the most part less seriously ill than those among the painters.

The drawing to be coloured represented in the foreground a group of young girls in a garden, three sitting or kneeling on a lawn, one talking to them from a deck-chair. In the background there were trees, grass, flowers, the sky and clouds. The experimental subjects were each given a box of Reeve's terrachrome crayons and asked to colour the drawing. The colours provided were light and dark red, light and dark yellow, light and dark green, light and dark blue, purple, mauve, black, brown, grey and white. The extent to which each colour was used was rated on a scale: 0, absent; 1, small amount; 2, fair amount; 3, considerable amount; 4, extreme amount. Differences in mean-ratings for each colour amongst schizophrenics, non-schizophrenics and nurses were tested by Student's *t*-ratio. The only significant differences were that the schizophrenics used purple and mauve, the non-schizophrenics light red, more abundantly than others.

The use of bright, dull, pale and heavy colouring and the total number of colours employed were examined but there were no significant differences. The way in which the colouring was executed was carefully observed in each individual. There were three basic levels of approach:

- (a) the colours were placed haphazard;
- (b) the colours were inserted according to realistic canons—"how it would look";
- (c) the colours were not only inserted realistically but were also patterned in an aesthetic scheme.

These might be mixed in the same drawing. Unrealistic colouring easily arose from haphazard placement, but in two instances (both schizophrenics) it was deliberate, once with patterning in order to gain strong aesthetic effects and once without patterning for negativistic reasons, "because it

wouldn't be like that." Haphazard placement occurred in 9 schizophrenics and 6 non-schizophrenics but was absent in the nurses; the difference between schizophrenics and nurses is statistically significant ($p = .018$). Aesthetic patterning occurred without significant differences (7 schizophrenics, 5 non-schizophrenics, 5 nurses).

REALISTIC AND UNREALISTIC COLOURINGS.

Separate parts of the drawing just described (skin of hands and faces, hair, trees and grass, sky, clouds) were isolatedly painted light red, light yellow, light green, light blue, purple, black and white. Each of these 35 possibilities was shown in turn in pre-determined random orders to the subjects, who were asked to say whether they liked or disliked it. Each subject was given an unrealistic score (maximum 15) for her total number of likings to the following: skin green, blue, purple; hair green, blue, purple; trees and grass red, yellow, blue, purple, white; sky green, purple; clouds green, purple. The mean unrealistic scores were 5.72 for schizophrenics, 3.33 for non-schizophrenics, and 2.00 for nurses. The schizophrenics differed significantly from the others ($t = 2.419$, df. 70, and 3.080, df. 52).

The subjects with an unrealistic score in excess of the schizophrenic mean were shown their unrealistic likings again and asked to explain why they liked colourings that were "unnatural." Their answers were classified as: *Generally indifferent*, expressing a weak feeling or concern about the matter; *reversing*, definitely stating that the colours were liked as a reversal of actuality; and *aesthetic*, adducing the artistic effect or the interest of the study in colour. The totals for these answers are shown in Table IV. It will be seen that

TABLE IV.—*Unrealistic colours: Reasons for liking.*

	Schizophrenics.	Non-Schizophrenics.	Nurses.	Totals.
Number above schizophrenic mean				
unrealistic score	18	8	4	30
Generally indifferent . . .	14	7	1	22
Reversing	3	0	1	4
Aesthetic	1	1	2	4

whilst reversal and aesthetic interest are determinants of an apparent liking for unrealistic colours, they are much less important than sheer indifference to the effect.

LIKING FOR ISOLATED COLOURS.

Cards of thick cartridge paper 10 cm. square were painted with the principal colours used by the patients in their paintings. These were presented in systematically randomized orders to the subjects, who were asked to rank them in order of preference. Stress was laid on the fact that it was liking for the colour in itself and not the colour as something to be worn that was in question.

The colours presented and the mean ranks for each class of subjects are shown in Table V. Statistically significant differences were :

- (a) the schizophrenics liked dark green better and white worse than did the non-schizophrenics ($t = 2.175$ and 2.182 , df. 70) ;
- (b) the schizophrenics liked mauve better and white worse than did the nurses ($t = 2.043$ and 2.327 , df. 52) ;
- (c) the non-schizophrenics liked dark green worse than did the nurses ($t = 2.544$, df. 52).

TABLE V.—*Colour preferences : mean ranks.*

Colours.	Schizophrenics.	Non-schizophrenics.	Nurses.
Dark red	6.72	6.39	5.33
Light red	7.36	7.00	7.22
Dark yellow	8.06	8.33	10.00
Light yellow	7.89	7.94	8.17
Dark green	6.03	8.22	5.89
Light green	6.42	7.11	7.17
Dark blue	6.72	7.61	6.56
Light blue	5.39	3.03	3.83
Purple	8.31	9.33	9.56
Mauve	8.03	9.81	10.44
Black	8.86	9.25	9.89
Brown	9.53	8.89	9.89
Grey	7.47	6.06	5.72
White	8.19	6.03	5.33

LIKING FOR COLOURS IN COMBINATION.

Combinations of colours were presented to the subjects by means of sets of cards identical with those used to present isolated colours. Each of the 14 colours was displayed as a temporary constant paired in turn with each of the 14 as values of the variable. There were thus 91 pairs of different colours, each being shown on two occasions, the first time with one colour, the second time with the other, as the constant. Each colour as constant was shown paired with itself as the variable ; this combination of course was not repeated. Three randomly determined orders were used for the presentation of the constants, and, within each constant, for the presentation of the variable. The variable colour was displayed alternatively to the right and to the left of the constant.

The subjects were asked to rate their liking for the colour-combinations on the following scale, using the simple symbolic equivalents named :

- Two ticks* : It gives me great pleasure ;
- single tick* : I like it ;
- nought* : I feel indifferent ;
- tick and cross* : I like and dislike it at the same time
- single cross* : I dislike it ;
- two crosses* : Most unpleasant ; I hate it.

It was emphasized that not the separate colours but their combination came into question and that this should be considered without reference to clothes.

By inspection it was evident that the schizophrenics made much more use of the "like" categories than did the others. If the double and single tick answers were added, the mean "like" scores were: schizophrenics 107.86, non-schizophrenics 99.33, nurses 79.56, the maximum possible score being 196. The schizophrenics differed very significantly from both the non-schizophrenics ($t = 3.709$, df. 70) and the nurses ($t = 3.696$, df. 52), and the non-schizophrenics differed significantly from the nurses ($t = 2.070$, df. 52). There were similar differences in the opposite direction with regard to "dislike" scores. There were no significant differences, however, in the summed "double" scores, the "indifferent" scores or the "like and dislike" scores.

For investigation of the 196 pairings it was convenient to take the total "like" scores (single and double ticks) as opposed to the total of the remaining categories. There were significant differences amongst schizophrenics, non-schizophrenics and nurses in 87 pairs. There were also significant differences amongst the three orders of presentation in the case of 38 pairs.

The differences between the three classes of subjects were carefully scrutinized for consistent principles that ran through them. The only principle found was that differences tended to appear if certain colours were present in the combination, either as constant or as variable, and not to appear if the colours were absent. No general tendency could be found for schizophrenics to show a greater liking for unpleasing combinations, as judged by any of the criteria recorded in the literature or otherwise suggested. No consistent principles ran through the differences between orders of presentation and they are almost certainly chance effects. Differences between colours as constants and as variables were examined but none were statistically significant.

In the circumstances the best way of dealing with the data of the colour combinations seemed to be to count the total number of "like" answers per individual for each colour combined either as constant or as variable. If the occasion that a colour occurred both as constant and as variable, i.e., when it was paired with itself, were counted once only, this gave 27 as the maximum number of "like" answers for each colour. Because of the significant differences amongst classes of subjects in their tendencies to give "like" answers, the 14 scores per individual were converted into standard measure in terms of their distribution in that individual. Statistically significant differences of means amongst schizophrenics, non-schizophrenics and nurses were as follows:

(a) the schizophrenics showed greater liking for combinations containing mauve and less for those containing white than did the non-schizophrenics ($t = 2.500$ and 3.490 , df. 70);

(b) the schizophrenics showed greater liking for combinations containing dark-red or mauve and less for those containing white than did the nurses ($t = 2.427$, 2.049 , 2.819 , df. 52);

(c) the non-schizophrenics showed greater liking for combinations containing dark-red and less for those containing dark yellow than did the nurses ($t = 2.520$, 2.375 , df. 52).

As each combination of different colours was presented twice it was of interest to compare the consistency of the subjects in their answers. An alteration from like to dislike or vice versa was counted as a major change of feeling. The schizophrenic mean change was 25.17, the non-schizophrenic 16.69, the nurses' mean change was 12.00, out of a maximum possible of 91. The schizophrenics differed very significantly from the other two classes ($t = 2.944$, $df. 70$, and 3.792 , $df. 52$).

STRENGTH OF FEELING.

Before rating the colour-combinations the subjects were questioned about their interest in colour, their painting experience, their attendance at art exhibitions and their knowledge of pictorial art as shown in the naming of favourite painters. There were no significant differences amongst the classes. After they had been shown the pairs of colours they were asked; "Would you say that colours rouse strong feelings in you or not? You've had a very good opportunity to decide that." Affirmative answers were given by 15 schizophrenics, 27 non-schizophrenics and 14 nurses; negative answers were given by 21 schizophrenics, 9 non-schizophrenics and 4 nurses. The schizophrenics differed significantly from the others ($p = .003$ and $= .010$).

ASSOCIATIONS WITH COLOURS.

The subjects were shown the fourteen painted cards in randomized orders and asked to say in one word what they associated with each colour or what it called to their minds. The associations were classified as:—natural objects; outdoor artificial objects; indoor artificial objects; clothes; body-parts (blood, eyes, etc.); death; religion; feelings; valuations; symbols; deviant (irrelevant or peculiar); blanks (failure to give an association); and miscellaneous.

In the total 14 associations there were significant or almost significant differences as follows:

- (a) schizophrenics associated more body-parts, fewer religious references, more feelings, valuations, symbols, and deviants, and fewer blanks than non-schizophrenics;
- (b) schizophrenics associated more clothing references, more body-parts, more deviants and fewer blanks than the nurses;
- (c) non-schizophrenics associated more clothing and religious references and fewer feelings, valuations and symbols than the nurses.

With regard to particular colours, however, there was no evidence of differences amongst the classes in the associations that they offered.

DISCUSSION.

In the actual paintings differences between schizophrenics and non-schizophrenics were inconsiderable compared with those between chronic and recent patients. There were quite a few differences between schizophrenics and non-schizophrenics in the supplementary experiments, but subsequent study of the

case-histories indicated that these non-schizophrenics were really nearer to recent than to chronic patients in their degree of illness and their isolation from the standards and values of everyday life. It is desirable, therefore, to leave on one side the question of schizophrenic reactivity and pose the differences as those between seriously disordered and much less seriously disordered persons.

One strongly supported finding was that the seriously disordered patients used or liked colours of the blue-red series (all hues, not merely mauvish-red) more than did other patients and normals.

A second well-supported finding was that the seriously disordered patients displayed weaker feeling in relation to colour than did the others. This was expressed in their own statements, in their readiness to say that they liked colour combinations, and in their greater inconsistency of feeling about colour combinations. The less seriously disordered patients were intermediate in this regard between the seriously disordered patients and the normals. This finding is in accord with the views of Kretschmer (1951) but contrary to those of Goldstein (1942), who stated that the influence of colours is increased in psychotics.

Other consistent findings were that the seriously disordered patients used grey and liked white less than did the others, employed heavy colouring more often and dull or pale colouring less often, and more often expressed a liking for unrealistic colourings. In the paintings but not in colouring a drawing, they made more use than the others of displeasing colour combinations.

There was no evidence to support the frequently made contention (e.g., Mosse, 1942; Emery, 1942; Birren, 1950) that schizophrenics have a particular fondness for yellow. There was likewise no evidence to support the view of Mosse and others that depressives make great use of black. There was some evidence of a tendency for the non-schizophrenic patients to like red better than did others, which might support Emery's view that depressives favour red, but within the non-schizophrenic sample there were no significant differences between depressives and psycho-neurotics in this regard.

It would appear that the central factor underlying all the peculiarities in the use of colour in painting by seriously disordered patients is a diminished feeling for colour or a weakened reactivity to it. To produce an appreciable effect they feel a need to use heavy or bold colourings; for the same reason they avoid dull or pale colourings. Displeasing colour combinations make less impact on them. A weakened reactivity to colour, in conjunction with impaired self-criticism, leads to haphazard placement and so to the production of unrealistic colourings. In rare instances, however, unrealistic colouring is deliberate, and may spring either from a negativistic motivation or from aesthetic experimentation. Avoidance of grey and relative dislike for white also seem to depend on a need for stronger stimulation to produce an effect, though the attitude to white may have some other explanation. The operative fact about the blue-red series seems to be that normal persons tend to dislike its hues, presumably because they simultaneously present the disturbing effect of red and the calming effect of blue (cf. Goldstein, 1939 and 1942; Kouwer, 1949), and hence occasion an experience of conflict. As the seriously

disturbed patients are not so responsive to colour they feel the unpleasant effects of this conflict less. At any rate it seems to be quite definite that the differences cannot be accounted for in terms of special associations with purple or mauve.

The physiological conditions on which the reduced reactivity to colour depends invite further investigation with reference, for instance, to the findings of Goldstein (1942) about the varying effects of differently coloured lights on motor activities, or those of Reeder (1944) that in maladjusted persons the retinal fields for colour show alterations and inversions.

SUMMARY.

1. An examination was made of the frequencies with which different colours were used and with which certain other characteristics appeared in the paintings of patients at Netherne Hospital.

2. Some supplementary investigations were conducted into the colour preferences and other attitudes to colours of mental-hospital patients, with nurses as a control group.

3. The principal findings were that seriously disordered patients used or liked colours of the blue-red series (purple and mauve) more than the others did, and displayed a weaker feeling in relation to colour. There were also some other consistent differences.

4. It is suggested that the central factor underlying all the peculiarities in the use of colour in painting by seriously disordered patients is a diminished feeling for colour or a weakened reactivity to it.

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A NOTE ON THE *A-B* RIDGE COUNT AND INTELLIGENCE.

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THE *a-b* ridge count, called the *a-b* count for short, is the number of epidermal ridges crossing or touching a fine straight line drawn joining the triradii *a* and *b* on the palm. The triradial point or the radiant when the former is absent is not included in the count. It was pointed out in a previous work (Fang, 1949) that on the assumption that the university students are more intelligent than the general population there is a consistent increase of the mean *a-b* count with intelligence. The results of the present study seem to agree with this finding.

The study was based on the palm prints of the following samples :

1. University students—238 females and 80 males, believed to be mainly British by descent.
2. Non-specified types of mental defectives—36 idiots, 133 imbeciles and 35 morons, known to be British by descent. Specified types of defectives such as mongoloid imbeciles, defectives due to birth injury or diseases, etc., were excluded.

The palm prints of the students are part of a collection made by Dr. Norma Ford Walker of the University of Toronto during the past some fifteen years, and those of the defectives are part of a collection made by Mr. A. Butler and myself at the Ontario Hospital School, Orillia, in the summer, 1950.

The results of this study are summarized in Table I. For convenience of comparison some results obtained from the previous study are included. It is noted here that in the previous study the average of the *a-b* counts on the right and left hands of an individual was used, while in the present the total instead of the average was used. For instance, when the right hand has an *a-b* count of 42 and the left hand 44, the total 86 instead of the average 43 is used. The increase of mean count with intelligence and the agreement between the present and the earlier studies can be seen from the following analysis :

1. The mean count of students in Ontario-British population is 85.32 ridges, while that of students studied in England is 84.31. The mean difference of 1.01 with a standard error of 0.89 is probably due to sampling variation.

2. The mean count of the non-specified types of the Ontario-British defectives is 80.62 ridges, while that of defectives studied in England is 79.23. As the mean difference of 1.39 has a standard error of 0.90, it can be ascribed to sampling variation too. A consistent sex difference in the mean count, higher in females than in the males, is present in the three grades of Ontario-

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TABLE I.—*The Mean a-b Counts and Percentage Frequencies of the Low Count Class in the University Students, General Population and Non-specified Types of Mental Defectives in Two Sets of Samples (One Studied in England and One in Ontario) Mainly British by Descent.*

Sample.	Sex.	Number.	Mean-s.d.	% of 78—
<i>Students—</i>				
1. England	F.	78	85.04-11.2	20.5
	M.	126	83.50-9.8	23.0
	Av.	204	84.31-10.4	22.1
2. Ontario	F.	238	85.37-9.8	23.5
	M.	80	85.16-11.7	26.3
	Av.	318	85.32-10.3	24.2
<i>General population—</i>				
1. England	F.	435	83.01-9.7	26.7
	M.	424	83.04-10.3	29.7
	Av.	859	83.03-10.1	28.3
<i>Mental defectives—</i>				
1. England	F.	201	78.56-11.2	51.2
	M.	258	79.84-12.2	49.2
	Av.	459	79.23-11.8	50.1
2. Ontario:				
Idiots	F.	17	84.53-11.1	29.4
	M.	19	80.47-10.8	47.4
	Av.	36	82.50-10.9	39.0
Imbeciles	F.	56	81.43-12.3	37.5
	M.	77	78.58-9.1	52.0
	Av.	133	79.77-10.4	45.8
Morons	F.	15	84.27-10.7	40.0
	M.	20	80.85-8.1	35.0
	Av.	35	82.31-9.0	37.1
Total	F.	88	82.51-11.6	36.4
	M.	116	79.28-9.1	48.3
	Av.	204	80.62-10.2	43.1

British defectives, though it was not observed in the corresponding English sample. The mean count is slightly, though not significantly, higher in the idiots and morons than in the imbeciles.

3. The mean count of the general British population studied in England is 83.03 ridges. This is significantly lower than that of the Ontario-British students, but higher than that of Ontario-British defectives. The mean difference between the British population and Ontario-British students is — 2.85, with a standard error of 0.64; that between the general British population and Ontario-British defectives is 2.41, with a standard error of 0.77.

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The palm prints of the mental defectives at Ontario Hospital School, Orillia, were collected thanks to arrangements made by Dr. Ford Walker and through the kind co-operation of the superintendent, Dr. Montgomery and his staff.

REFERENCE.

FANG, T. C., "A Comparative Study of the a-b Ridge Count on the Palms of Mental Defectives and the General British Population," *J. Ment. Sci.*, 1949, **95**, 401.

Part II.—Reviews.

Genetic Neurology. Edited by P. WEISS. University of Chicago Press, 1950. Pp. 239. Price 37s. 6d.

This volume presents a series of chapters written by members of the first International Conference on the Development, Growth and Regeneration of the Nervous System held in March, 1949, at the University of Chicago, sponsored by the International Union of Biological Sciences and financed partly by UNESCO and partly by the Rockefeller Foundation. The subject matter as a whole is covered by the introduction of a new subject-title—Genetic Neurology.

As is to be expected a great deal of the subject-matter is severely technical, but it does give an excellent picture of present-day neuroembryology, using the term in its widest sense, and extending from spectroscopic studies on nerve cells to regeneration in human peripheral nerves, from motion pictures showing the movements of neurones and neuroglia in tissue cultures to the reflexes of mammalian embryos and fetuses.

Although highly specialized, the book is very readable and presents an excellent summary of our knowledge of a rapidly developing field.

G. W. T. H. FLEMING.

The Transmission of Nerve Impulses at Neuroeffector Junctions and Peripheral Synapses. By A. ROSENBLUETH. London: Chapman & Hall, Ltd., 1951. Pp. 325, and 98 figures. Price 48s.

This is an extremely well-documented and careful account of the chemical transmission at the junctions of motor nerves and striated muscles and at the synapses of autonomic ganglia.

The author is of the opinion that there is no satisfactory alternative to the chemical theory of synaptic transmission. He looks on acetylcholine as the essential transmitter with potassium ions as important adjuvants, and at the same time the spike potential determines the release of acetylcholine.

The book is divided into two sections, the first dealing with transmission at autonomic neuroeffector junctions, and the second with transmission at peripheral synapses, and is a most important contribution to our knowledge of the physiological action of acetylcholine.

G. W. T. H. FLEMING.

Dementia Praecox or the Group of the Schizophrenias. By EUGEN BLEULER. Translated by JOSEPH ZINKIN. London: Allen & Unwin, 1951. Pp. 548. Price 63s.

This volume is a translation of Bleuler's large monograph on dementia praecox which appeared in 1911 as a volume of Aschaffenburg's *Handbook*. It is a pity that it has had to wait nearly forty years before being translated into English. Those of us who read Bleuler's textbook when it appeared in the 1920's were much impressed with his views, and particularly those on a clinical condition which was so often neither a dementia nor precocious in its origin and which he called the "schizophrenias," a term which has come into almost universal use to-day. This rather bulky volume of more than five hundred pages well repays the time spent in wading through it even forty

years after it was published, and even considering the advances that have been made in psychiatry since then. It is one of the great classics of psychiatry.

G. W. T. H. FLEMING.

Soviet Psychiatry. By JOSEPH WORTIS. Baltimore: The Williams & Wilkins Co., 1950. Pp. 314. Price 38s. 6d.

This is a most "illuminating" account of Soviet Psychiatry and makes almost incredible reading.

The author has gone to the greatest pains to provide his readers with an account of psychiatry and psychology as they are presented in Soviet medical journals, and it is by these only that Soviet psychiatry can be judged.

It is almost impossible to credit that the *principle of partisanship* must apply to psychology. "Soviet psychology must reflect the influences of the new society in its methods of work and in its theories. Soviet psychology must therefore divest itself of foreign or ancient principles no longer appropriate to the new order," or that according to Rosenshtein, "Mental hygiene in the capitalist countries is mostly a palliative, and is at the same time a ruling class weapon designed to combat the militant activity of the working masses by involving them in this bourgeois philanthropic movement. In the U.S.S.R. mental hygiene has an entirely different class character: Socialist construction creates healthy conditions of life and work, and thus eliminates the tensions which cause so many neuropsychiatric disturbances."

"Political insights and a solid class orientation are regarded as indispensable pre-requisites to a realistic approach to life, to a sound social integration or to wholesome psychological development."

The Marxist apparently regards impartiality as at best an illusion and at worst a fraud.

The reader will find it very difficult to separate the wheat from the tares in this most interesting book. It is a psychological study of what psychiatry should *not* be. One feels that objective work and criticism in the U.S.S.R. simply do not exist and Wortis has carried out a very useful piece of work in drawing our attention to the "insanity fair" behind the iron curtain.

G. W. T. H. FLEMING.

The Annual Review of Psychology. Vol. II. Edited by C. P. STONE. California: Stanford, 1951. Pp. 388. Price \$6.

The second volume of this series maintains the high standard set by its predecessor. It is of course rather more of a book of reference, but many of the chapters have an intimate connection with our speciality, some much more than others. At the beginning and end of the book quite aptly, we find chapters on child psychology and gerontology, both subjects very much to the front to-day; both chapters are well done.

Its most interesting chapters are those dealing with personality and with abnormalities of behaviour.

G. W. T. H. FLEMING.

The Cerebral Cortex of Man. By W. PENFIELD and T. RASMUSSEN. New York: The Macmillan Company, 1950. Pp. 248 and 121 figures. Price 48s. 6d.

Most of the contents of this book originally appeared as the Lane Medical Lectures in 1947, and deal with work carried out by the senior author during a period of nearly twenty years. The cortex was stimulated under local anaesthesia and the patients gave their versions of what they felt was happening.

The book may well be regarded as a milestone on the road towards a fuller and more accurate knowledge of cerebral cortical function, but it is only one

of the early milestones. Present-day cerebral physiology is progressing rapidly by means of modern techniques together with the knowledge acquired from so-called psychosurgery, and this book serves to crystallize many of our ideas on cortical function, but much remains to be done.

It is a pity to see the word "amentia" used in a book of this standing. In Italy *amenza* is confusional insanity, and in Holland also amentia is confusional insanity, whereas in the old-fashioned days of Shaw Bolton, in this country by amentia was understood mental deficiency or what is to-day subsumed under the term oligophrenia. It is a pity to see amentia used to mean "progressive loss of intellectual function" of an extreme degree. The word is better forgotten.

G. W. T. H. FLEMING.

The Neurologic Examination. By R. N. DE JONG, M.D. London: Cassell & Co., Ltd., 1951. Pp. 1079 and 299 figures. Price 110s.

This is an excellent book. It is a book of neurological diagnosis based on abnormalities of structure or functions of the various parts of the nervous system. Naturally in a book of this size and nature there is a heavy emphasis on anatomy and physiology throughout. The different diagnostic procedures are well described and are correlated with the symptoms to be found. At the same time the more modern and technical procedures such as electroencephalography, X-ray examination and psychological testing are very wisely left to the monographs dealing with them.

Although the volume is of nearly eleven hundred pages, a great deal has had to be omitted, and the same applies to the bibliography at the end.

The section dealing with the cranial nerves is possibly the best chapter in the book, followed closely by that on the motor system, otherwise it is difficult to pick out any chapter as superior to any other.

G. W. T. H. FLEMING.

Emotions and Clinical Medicine. By S. COBB. London: Chapman & Hall, 1950. Price 15s.

What could be more welcome to the psychiatrist to-day than a critical survey on the anatomy, physiology, psychology and sociology of emotions, especially when the survey is made by a clinician of the distinction and experience of Stanley Cobb? In recent years emotion has been adopted as a stop-gap concept in psychosomatic medicine. Cobb has handed over the conceptual problem to J. R. Reid, a philosopher, who has written a short, lucid introductory chapter on semantics and definitions, which deserves careful reading by all those who have placed too high hopes in semantics as a way of escape from the ambiguities of psychiatric vocabulary. The rest of the book is an enlarged version of the Salmon Lectures delivered by Cobb in 1949. The author stresses his long-standing interest in psychosomatic medicine, and he includes clinical case material and the results of researches from his Department at the Massachusetts General Hospital in Boston. One chapter is devoted to case studies; anorexia nervosa is exemplified as a psychosomatic problem without, however, much new light being shed on its nature. These factual observations are obviously included so as to counterbalance the excess of theoretical and philosophical writing which American workers have produced on psychosomatics. These workers seem to have taken over the role formerly played by certain German writers with much hypothetical verbosity and little observational background. Cobb deals with some workers critically, e.g., with the work on personality by Flanders Dunbar, but he seems too tolerant and insufficiently discriminating with others from whom lengthy, obscure passages are quoted. Altogether, the second part of the book, in which the clinical applications are discussed, is disappointing because a clear

attitude to decisive problems is absent. It certainly does not compare with the earlier chapters in which the contribution to emotions of the different parts of the central nervous system and of the endocrine glands in health and disease is recorded. Here, the high academic standard one would expect is kept up throughout, and a full account of our knowledge can be found, at least as far as it is represented in the literature in English. Regrettably, there is an almost complete absence of reference to work published in French and German, especially on the classification of emotions and their relation to cerebral lesions.

To sum up: Cobb's book on the rôle of the emotions in medicine is not the critical survey that can be handed to the interested student, but rather a physician's collections of personal impressions garnered from the literature and the clinic.

W. MAYER-GROSS.

The Sober Truth. By LINCOLN WILLIAMS. Distributed by Edgar Backus, Leicester. Price 6s.

This small book gives a clear and straightforward account of the problem of alcoholism. It outlines various patterns of alcoholic consumption, and emphasizes that the true alcoholic is a compulsive drinker who cannot revert to drinking in moderation and for whom a single drink is like "putting a lighted match to petrol." Other chapters describe briefly and in simple terms the psychological and physical effects of alcohol, the influence of heredity and the legal aspects of alcoholism. The last three chapters are devoted to treatment, and here the emphasis is almost entirely on the activities of "Alcoholics Anonymous," which the author describes as "an outstanding form of . . . group therapy."

The Sober Truth has been written for the alcoholic and his relatives and can be confidently recommended to them. Further editions should include a bibliography of the papers on alcoholism mentioned in the text.

J. HARPER.

Hay-Fever. By JOHN FREEMAN, D.M.Oxon.

The subject of this book is one with many sides to it, yet heretofore the medical public has been regaled with many articles and books written from a single standpoint instead of taking into consideration all possible synergic factors.

Here, on the other hand, three chapters (covering 52 pages) are taken up with the emotional factor in the causation of hay-fever, and all through the book the note of psychosomatic synergy presents itself.

The book is thus of an unusual character, and this would, by itself, be a reason for recommending it, but it is worth much more than that would suggest. Indeed, I would give it to a young doctor on the day of his graduation with the request that he preserves it as a bedside book for his whole professional life. Dr. Freeman, like his great teacher Sir Almroth Wright, has that touch of genius which turns trivial evidence into valuable conclusions: the gift, that is to say, of binocular vision—seeing the objective picture and accepting it at its true value, while the subjective side is maintained with the same validity of evidence.

The author shows a disarming combination of assurance and of tentative reservation. He is convinced by his own argument only after much conflict and much sifting of evidence.

Here is a highly significant passage (Chap. 3): "Single Cause Fallacy—I speak deliberately of the 'causal mechanism' and not of 'the cause.' Much medical controversy and misunderstanding is based on what may be called the Fallacy of the Single Cause." Dr. Freeman sets forth seven causative

factors which he calls "manipulable." Then our author takes a great plunge: "I would go further and guess that all seven causes are necessarily involved in every case to a greater or less extent." There are not many even amongst the most zealous psychosomatic preachers and teachers who would endorse without reservation this universal doctrine. The seven causative factors are:

- (a) Heredity—(hardly treatable).
- (b) Idiotoxin—(e.g., grass pollen in hay fever).
- (c) Idiocyte—(sensitiveness to the idiotoxin).
- (d) Serious Leak—(that is, from the blood vessels).
- (e) Trauma—(the localizing factor).
- (f) Emotions—(always play a part, but *only* a part in causation).
- (g) Bacterial—(acts in various ways).

Taken all round this book is worthy of immortality as a classic, because the psychosomatic gospel is here presented in its dual aspect—that is to say, in describing the effect of emotional reaction on the symptom as well as the toxic effect upon the patient's mentality. The author is indeed to be congratulated on compounding a book that reveals his own scientific judgment and open-mindedness. Finally, this is a book that only reactionaries will have the courage to condemn. We hope it will have the circulation it merits and pass from edition to edition as it clearly deserves.

H. CRICHTON-MILLER.

Modern Abnormal Psychology. Edited by W. H. MIKESELL. New York: Philosophical Library, 1950. Pp. 880. Price \$10.00.

This is an erudite and eclectic book, written by thirteen psychiatrists and twelve psychologists for the benefit of students and the general public.

The chapters vary in worth and style, but Chapter 2, on "Psychotherapy: Outline of its History and Present Situation," by Drs. Grotjahn and Gabe, excels in both. Some chapters are pompous, but all are realistic, even if they also read in places like a guide-book. One chapter alone has 106 references, and over 500 persons are mentioned at the end of the book in an Index of Names. Yet the book is modest about our knowledge of abnormal psychology; as Albert C. Voth, Ph.D., says in the last chapter, "we are still groping in a pre-dawn darkness."

American spelling is of course used, and so are words such as "acculturation," and unexpected phrases punctuate the book in a startling manner—a patient struggling to succeed in life is described as "punch drunk" with failure. A doctor or psychologist treats his "client" in an "office."

The book is printed clearly on good paper.

C. E. H. TURNER.

The Law Relating to Mental Treatment and the Health Service. By HAROLD BERRY. Churchill, 1951. Pp. 121.

This little book is reasonably accurate, and contains much useful information about the law governing the treatment of mental illness and mental deficiency. It is, however, a little difficult to assess for whom it is intended. If addressed to those requiring full details of the law in connection with their professional work in relation to patients in or going into mental hospitals, then one must deplore certain glaring omissions, chief of which we would mention the position of voluntary patients losing volition and of temporary patients regaining it. No mention is made in the voluntary patient section of the fact that he can leave on his own notice, nor is the method of extending temporary treatment described. The rules and procedures to be observed when patients die in hospital are nowhere to be found (except for burial arrangements), while there is no reference to divorce on grounds of incurable insanity.

If, on the other hand, the book is intended for the more general reader, then the order of the various sections seems unfortunate. Rather than plunge straight into the multiple procedures for certification in Chapter II and leave the question of voluntary and temporary treatment till late in Chapter IV, one would have thought that a more natural presentation would have been to deal first with the admission of the willing patient, next the one unable to will, then the certified case, and finally the "short order" method in instances of urgency. Again, one doubts the desirability of giving such a detailed description of the regulations concerning restraint, or of unduly emphasizing discharge under Section 72, while Section 79 is only mentioned later in a casual manner. Surely the recovered case is likely to be discharged as such by the hospital authorities themselves and the unrecovered case by the Committee to the care of relatives, so that Section 72 should not be held up as the main means of discharge so much as a last resort when the more usual methods have failed.

In any case the arrangement of the book is most infuriating. To find "VOLUNTARY PATIENTS" as a main heading followed by "Visitation by Commissioners," "Burial of Patients" and "Utilisation of Patients' Labour" as apparently subsidiary headings, while not necessarily leading to a belief in some subtle connection between the voluntary status, work and early demise, is nevertheless confusing. Some chapters seem to have a principal title, others not. Again, "Discharge" (one of the points of major interest) appears under "Miscellaneous Provisions" together with "Debts" and "Penalties," and so on.

A good small book on this subject is much needed. That is why we have been at some pains to stress what seems to us the inadequacies of this volume, in the hope that in future editions the subject-matter might be so rearranged as to be clear and helpful, instead of giving the impression that the galley-proofs have been thoroughly mixed up before the final printing.

J. ERNEST NICOLE.

Thomas W. Salmon, Psychiatrist. By EARL D. BOND, M.D. Chapman & Hall, Ltd., 1950. Pp. 237.

This biography of one of the great figures of American psychiatry is of considerable value. It presents a vivid picture of Salmon and his work both at home and with the A.E.F. in 1917-19. Of particular interest is the description of his association with Clifford Beers and his participation in the birth of the Mental Hygiene movement. The book includes a list of Salmon's writings.

One cannot, however, leave without comment a footnote on page 51 that seems not only extreme, but an anticipation of defeat that one can surely hope will be disproved in the light of future experience. The text describes Beers' observation of mental hospital conditions and how "he discovered and vividly described the attendants into whose care most mental patients are delivered. Most of them in his opinion were ignorant, brutal and incompetent." Here is interposed the unfortunate footnote, to the effect that "this discovery, made in 1908, was made again in 1948 and probably will be made again in 1988."

J. ERNEST NICOLE.

Part III.—Bibliography and Epitome.*

ACTA NEUR. PSYCHIAT BELG.

VOL. LI.

MAY, 1951.

Painful Akinesia, etc. <i>Lopez-Ibor, J.</i>	287
Neurological Manifestations of Vaquez's Disease. <i>Liessens, P.</i>	300
Phenylacetylurea in the Treatment of Epilepsy. <i>Sorel, L., et al.</i>	309
Aseptic Meningitis from the Rupture of a Cholesteatoma. <i>de Lehoczky, T.</i>	319

JUNE.

Cirroid Aneurysm of the Right Frontal Lobe. <i>Gros, C., and Martin, G.</i>	337
Cavernous Angioma of the Brain. <i>Furtado, D., et al.</i>	343
The Treatment of Intracranial Aneurysms. <i>van Gehuchten, P., et al.</i>	357
The Semiology and Evolution of Intracranial Aneurysms in Syphilitics. <i>Ketelaer, Ch. J.</i>	362

JULY.

The E.E.G. in Encephalo-trigeminal Angiomatosis of Sturge-Weber-Krabbe. <i>Radermecker, J.</i>	427
An Abortive Case of Encephalo-trigeminal Angiomatosis. <i>André, M., and Hermans, R.</i>	452

ACTA PSYCHIAT. NEUR. SCAND.

VOL. XXVI.

1951.

Experimental Studies on Electro-shock Treatment. <i>Lunn, V.</i>	7
Lung Tuberculosis Precipitating Reactive Psychoses. <i>Nielsen, C. K.</i>	49
The Presence of Histamine and Noradrenaline in Nerves as Related to their Content of Myelinated and Unmyelinated Fibres. <i>Rexed, B., and von Euler, U. S.</i>	61
Hypnotic Induction by Means of Folding Hands. <i>Wagner, F. F.</i>	91
On Manic Depressive Psychosis and Neurosis. <i>Zahle, V.</i>	95

ACTA PSYCHIAT. NEUR. SCAND., SUPPL. 74.

1951.

On the Pathogenesis of Multiple Sclerosis. <i>Fog, T.</i>	22
The Clinical Aspects of Disseminated Sclerosis. <i>Muller, R.</i>	32
Experience of A.C.T.H. and Cortisone Treatment in Some Organic Neurological Cases. <i>Jönsson, B., et al.</i>	60
Experience with Hormone Treatment in some Organic Nervous Diseases. <i>Jönsson, B., et al.</i>	66
Experiences with Various Headache Tests. <i>Dalsgaard-Nielsen, T.</i>	111
Treatment of Epilepsy with Mesantoin and Phenantoin. <i>Lund, M., and Nørgaard, K.</i>	118
One-sided Cerebral Ventricular Dilatation in Cryptogenic Epilepsy. <i>Simonson, H.</i>	120
On the Correlation between Clinical Type of Seizure and E.E.G. Paroxysmal Pattern in Epilepsy. <i>Saxe, L.</i>	124
The Function of Adrenal Cortex in Epileptics. <i>Rattenborg, C.</i>	129

* A number of abstracts in this section are reproduced from *Chemical Abstracts*. To the Editors of this Journal we extend our grateful thanks.

The Anatomy and Pathogenesis of Cortical Brain Atrophies. <i>Brodal, A.</i>	140
Atrophia Cerebri. <i>Hermann, K.</i>	165
On Diffuse Brain Sclerosis and its Histopathogenetic Relationship, Especially to Amaurotic Idiocy. <i>Einarson, L.</i>	180
Alzheimer's Disease—Pick's Disease. <i>Sjögren, H.</i>	190
The Course and Relations of the Spino-thalamic Tract in Man. <i>Glees, P., and Bailey, R. A.</i>	199
The Motor Cortex of the Macaque. <i>Glees, P., et al.</i>	207
Brain Atrophy in a Psychiatric Clinic Diagnosed by Pneumoencephalography. <i>Wagner, F. F.</i>	212
On Abdominal Reflexes. <i>Monrad-Krohn, G. H.</i>	216
E.E.G. in Simple Concussions. <i>Dalsgaard-Nielsen, T., and Hertz, H.</i>	233
Traumatic Cephalalgia in Concussion of the Brain. <i>Røntorp, S.</i>	235
The Treatment of the Post-concussion Syndrome. <i>Silfverskiöld, B. P.</i>	264

ACTA PSYCHIAT. NEUROL., SUPPT.

Specific Dyslexia. <i>Hallgren, B.</i>	No. 65
Changes in Circulation Through the Anterior Cerebral Artery. <i>Ethelberg, S.</i>	75

AM. J. MENT. DEF.

VOL. LVI.	JULY, 1951.
Research Techniques in Mental Hygiene. <i>Dayton, N. A.</i>	18
Problems in Helping Parents of Mentally Defective and Handicapped Children. <i>Scheimo, S. L.</i>	42
Electrodiagnosis in Cerebral Palsy. <i>Ganger, A. B.</i>	145
The Delayed Reaction in Mental Defectives. <i>Pascal, G. R., et al.</i>	152
Mosaic Patterns of Institutionalized Mental Defectives. <i>Shotwell, A. M., and Lawrence, E. S.</i>	161
A Study of Concept Formation by Means of the Object Sorting Test with Subnormals. <i>Stacey, C. L., and Portnoy, B.</i>	169
A Study of the Wechsler-Bellevue Intelligence Scale and the Vibs Short Form in an Institute for the Mentally Deficient. <i>McKenzie, R. E.</i>	174
A Proposed Correction for the Confounded Effects of Cultural Variation in Intelligence Quotients. <i>Gellerman, S., and Hays, W.</i>	177

AM. J. ORTHOPSYCHIAT.

VOL. XXI.	JULY, 1951.
Metapsychology and the Right to Believe. <i>Cole, L. E.</i>	461
Symposium on Genetic Psychology. <i>Werner, H., et al.</i>	472
The Popular Response in Rorschach Records of Normals, Neurotics and Schizophrenics. <i>Molish, H. B.</i>	523
Some Contributions of Psychological Tests to Therapeutic Planning. <i>Reichard, S.</i>	532
Patterns of Social and Cognitive Outlook in Children and Parents. <i>Frenkel-Brunswick, E.</i>	543
Treatment of Childhood Schizophrenia in a Child Guidance Clinic. <i>Fabian, A. A., and Holden, M. A.</i>	571
Changes in Human Figure Drawings by Patients who Recover from Regressed States. <i>Modell, A. H.</i>	584

AM. J. PSYCHIAT.

VOL. CVII.	JUNE, 1951.
Clinical Language Rehabilitation of the Veteran. <i>Freud, E. D.</i>	881
Emotional Problems of Maladjustment in Children with Reading Difficulties. <i>Odenwald, O. D., and Shea, J. A.</i>	890
Inference Testing in Psychotherapy. <i>Reid, J. R., and Finesinger, J. E.</i>	894
Psychiatric Symptoms and Syndromes in Parkinson's Disease. <i>Schwab, R. S., et al.</i>	901

Electromyographic Recording During Interview. <i>Davis, F. H., and Malmo, R. B.</i>	908
The Hypnotic and Hypnotherapeutic Control of Severe Pain. <i>Rosen, H.</i>	917
Prognoses and Psychological Scores in E.C.T., Psychosurgery and Spontaneous Remission. <i>Scherer, I. W.</i>	926
Sterilization in Preventive Psychiatry. <i>Gamble, C. J.</i>	932

VOL. CVIII.

JULY.

The Individual Psychiatrist and Social Psychiatry. <i>Whitehorn, J. C.</i>	I
*A Progress Study of Lobotomized and Control Patients. <i>Friedman, S., et al.</i>	10
Psychiatric Symptoms Associated with Intracranial Neoplasms. <i>Soniati, T. L. L.</i>	19
The Conception of Wholes and Parts in Early Infantile Autism. <i>Kanner, L.</i>	19
Involitional Illnesses. <i>Tait, C. D., jun., and Burns, G. C.</i>	27
The Psychodynamics of Failure in Therapy. <i>Koren, L., et al.</i>	37
Mental Deficiency as a Basic Discipline in the Training of a Psychiatrist. <i>Gibson, R.</i>	42
Acute Pulmonary Changes During Insulin Coma Therapy. <i>Cogan, S., and Gross, R. J.</i>	44
*Changes in the Body Weight of Schizophrenic Patients Following Pre-frontal Lobotomy. <i>Buck, C. W., et al.</i>	46
Neurophrenia. <i>Doll, E. A.</i>	50
Heredity and Mental Tests. <i>Halperin, S. L., and Guensberg, M.</i>	54

A Progress Study of Lobotomized and Control Patients.

Previous reports in the literature have crystallized quite well the results effected by frontal lobotomy in the treatment of the major psychoses. The authors' present investigation, which deals particularly with dementia praecox, gives further support to previous conclusions. Apparently one can anticipate that some 50 to 60 per cent. of appropriately selected patients will exhibit significant improvement following frontal lobotomy, with approximately equal division between levels of moderate improvement and of marked improvement. There appear to be relatively few relapses with the passage of time—at least within a 2-year period—and, statistically, these relapses are compensated by other cases that exhibit their optimal improvement after a year or more of post-operative interlude. In general, results are somewhat better in affective disorders and other nonschizophrenic conditions than in dementia praecox. Among the latter, best results are observed in the mixed and paranoid subgroups. Symptoms related to tension and depressive states, emotional aggressiveness and hyperkinetic behavioristic features are most amenable to lobotomy. This lends support to the implication emphasized by other investigators that the clinical results of psychosurgery are attributable to its influence on emotionally charged psychic phenomena, presumably through interruption of appropriate thalamic radiations. The authors' discharge rate of some 37 per cent. agrees closely with the statistics of other large series of cases. The most frequent significant complication, convulsive seizures, appears to occur in some 10 to 15 per cent. of patients. It is generally accepted that this is not a burdensome complication; it is readily controlled by anticonvulsant therapy. Operative mortality appears to range around 2 to 3 per cent.

The problem of controls has been of particular interest to the authors in their study. It was decided that the most satisfactory controls would be patients who, like the operative group, had been selected for lobotomy according to currently recognized clinical criteria, but on whom operation could not be performed because of refusal of permission by the family. The two groups were well matched from the standpoint of various factors, especially in the pertinent features of diagnostic grouping and symptomatology. Although the mean duration of hospitalization was somewhat lengthier in the control group, the difference was not sufficiently pronounced to exert a significant effect on the final results. The great majority of both groups had been hospitalized longer than two years—a temporal point that appears to be critical from the standpoint of recovery spontaneously or by the aid of therapeutic measures other than lobotomy.

In contrast to the operative group, there was practically no change in the status of the control group at the termination of the two-year observation period. Only 3 per cent. exhibited significant improvement—none at a level superior to moderate improvement. No significant long-term improvement was achieved in this chronically ill control group by the use of shock therapies. Only 2 per cent. were able to leave the hospital, and one of these patients required rehospitalization within a relatively short time. It seems evident, particularly with respect to dementia praecox, that the course of the illness will be well crystallized before the end of the second year of hospitalization. Improvement, either by spontaneous means or by the use of shock therapies, is rare after this point, and it would seem fruitless to delay psychosurgery in appropriate cases much beyond this time. Comparative results in the authors' two groups lead to the inevitable conclusion that lobotomy exerts a beneficial effect that is not achieved by other means in cases of chronic mental illness. (Authors' abstr.)

Changes in the Body Weight of Schizophrenic Patients Following Prefrontal Lobotomy.

1. In this series of schizophrenic patients there was no consistent group change in weight prior to the sixth month after lobotomy.
2. At the sixth post-operative month the patients as a group showed a small but significant weight increase. This arose principally from a marked weight gain on the part of a small group of patients.
3. The marked weight gains that occurred in certain patients post-operatively led, for the most part, to a resumption of a normal weight rather than to the development of obesity.
4. Separate analyses of the improved and unimproved groups indicated a trend toward weight gain in the improved patients, and a trend toward weight loss in the unimproved patients.
5. The post-operative retraining program did not appear to be responsible for the weight changes after lobotomy.
6. These findings indicate that an increase in weight does not necessarily follow the operation of prefrontal lobotomy. It is suggested that those patients who do gain weight on a controlled diet do so as a result of the improved appetite that accompanies amelioration of their mental symptoms. There is no indication from these observations that lobotomy produces any metabolic change leading to abnormal weight increase. The findings, instead, would confirm the prevalent belief that obesity following lobotomy results from uncontrolled eating during the post-operative period. (Authors' abstr.)

AUGUST.

The Assessment of Mental Health. <i>Eaton, J. W.</i>	81
Psychological Tests in the Selection and Placement of Psychiatric Aides. <i>Yerbury, E. C., et al.</i>	91
The Conversion of Passivity in its Normal Self-assertion. <i>Cameron, D. E.</i>	98
The Role of the General Hospital in the Care of the Mentally Ill. <i>Gayle, R. F., jun.</i>	103
Atropine Toxicity in the Treatment of Mental Disease. <i>Forrer, G. R.</i>	107
Psychiatric Interview Experiences with Negroes. <i>St. Clair, H. R.</i>	113
Inferiority Feelings and Hostility. <i>Saul, L. J.</i>	120
The Diagnosis of Schizophrenia. <i>Langfeldt, G.</i>	123
Corrective Emotional Experiences in Group Therapy. <i>Frank, G. D., and Ascher, E.</i>	126
Diagnosing Mental Deficiency in Psychotics. <i>Drubin, L., and Singer, M.</i>	138

SEPTEMBER.

A Criticism of the Terms "Psychosis," "Psychoneurosis" and "Neurosis." <i>Bowman, K. M., and Rose, M.</i>	161
The Role of the Psychiatric Nurse in the Newer Therapies. <i>Bennett, A. E., and Eaton, J. T.</i>	167
A Survey of Conditions of Private Psychiatric Practice Throughout the United States and Canada. <i>Muncie, W., and Billings, E. G.</i>	171

Culture, Society and Personality. <i>Brown, G. G.</i>	173
A Survey of Szondi Research. <i>Guertin, W. H., and McMahon, H. G.</i>	180
Psychiatric Observations under Severe Chronic Stress. <i>Kral, V. A.</i>	185
Intensive Electroshock Treatment with Reiter Apparatus. <i>Frosch, J., et al.</i>	204

AM. J. PSYCHOTHER.

VOL. V.

APRIL, 1951.

Supervision of the Psychotherapeutic Process. <i>Wolberg, L. R.</i>	147
What Makes People Change. <i>Auerbach, J. G.</i>	172
The Concept of Adult Libido and the Lear Complex. <i>Pauncz, A.</i>	187
The Use of Pictorial Images in Group Therapy. <i>Prados, M.</i>	196
Pathological Boredom and Inertia. <i>Bieber, I.</i>	215
Nightmares of Cannibalism. <i>Fodor, N.</i>	226

JULY.

An Hypothesis Regarding the Scope and Limitations of Psychotherapy. <i>Hoffmann, G.</i>	339
First Aid in Acute Panic States. <i>Meerloo, J. A. M.</i>	367
Current Trends in Group Psychotherapy. <i>Wender, L.</i>	381
The Rorschach Examination and Psychotherapy. <i>Wender, L.</i>	405

AN. PORT. PSIQUIAT.

VOL. III.

MAY, 1951.

The Psychopathology of Delusions. <i>Fernandes, B.</i>	6
The Application of Mental Tests in Clinical Psychiatry. <i>Amaral, A.</i>	9
Anatomo-physiology in the Light of Lobotomy and Topectomy. <i>Flores, A.</i>	15
Indications for Shock Methods in Psychiatry. <i>Furtado, D.</i>	17
Present Tendencies of Psychoanalysis in Portugal. <i>Pereira, G.</i>	20
Evolution and Present Tendencies of Psycho-analysis. <i>Searba-Dinis, J.</i>	23
Genetics and Eugenics. <i>Ilharco, F.</i>	25
Some Considerations on the Pathological Mechanisms of Delusions. <i>d'Oliveira, C.</i>	27
Treatment of Alcoholism by Antabuse-type Drugs. <i>Furtado, D., et al.</i>	29
Psychotic Reactivation by Antabuse. <i>de Oliveira, P.</i>	34
The Importance of Mental Tests in Psychiatry. <i>d'Oliveira, C.</i>	38
The Study of Psychopathology and of Depersonalization. <i>Searba-Dinis, J.</i>	40
Cerebral Anatomo-physiology and Psychic Function in Pre-frontal Leucotomy. <i>Fernandes, B.</i>	46
Anatomo-physiology in the Light of Lobotomy and Topectomy. <i>Flores, A.</i>	61
Endocrine and Vasomotor Therapeutics in Psychiatry. <i>Furtado, D.</i>	64
Therapeutic Aspects of Leucotomy. <i>Fernandes, B., et al.</i>	75
The Myokinetic Test in Leucotomised Patients. <i>Mendes, F.</i>	80
Psychomotor Reaction-times and their Clinical Significance in Leucotomised Patients. <i>Amaral, A.</i>	83
Insulin and Insulin-cardiazol in Mental Disease. <i>Polonio, P.</i>	87
Gastro-duodenal Ulcer in Psycho-somatic Medicine. <i>Soeiro, L. N.</i>	90
Constitutional Typology in the Psychoses. <i>Polonio, P.</i>	92
The Definition of the Term " Social Psychiatry "	95
Treatment of Depressions by Succinic Dinitrile. <i>Furtado, D.</i>	96
Evolution and Devolution of Function in Psychopathology. <i>Fernandes, B.</i>	102
The Influence of War on the Youth of Countries where there has been no War. <i>Fontes, V., et al.</i>	104
The Brain and Mental Life. <i>Kleist, K.</i>	112
Methods of Work and Results from Investigation by the Kretschmer School. <i>Koch, G.</i>	120
The Mode of Action of Leucotomy. <i>Yahn, M.</i>	151
Psychological Tests and the Mental Clinic. <i>Wallon, H.</i>	163

ANN. MED.-PSYCHOL.

VOL. CIX.

JUNE, 1951.

Confession. <i>Ley, A., and Versele, S.</i>	I
Biological Concepts of Delinquency and Intervention of the Frontal Lobe in Delinquents. <i>Bachet, M.</i>	22
Cerebral Proteins. <i>Chatagnon, C.</i>	57

JULY.

Thought in Schizophrenic States. <i>Burstin, J.</i>	129
A Critical Study of the M.M.P.I. <i>Gayral, L., et al.</i>	166

ARCH. NEUR. PSYCHIAT.

VOL. LXV.

JUNE, 1951.

*Dandy's Striatal Theory of "The Center of Consciousness." <i>Meyers, R.</i>	659
Encephalopathy Associated with Acute Diffuse Platelet Thrombosis. <i>Hauser, A., et al.</i>	672
Effects of A.C.T.H. on Cerebral Blood Flow and Oxygen Consumption. <i>Alman, R. W., and Fazekas, J. F.</i>	680
Familial Occurrence of Tuberous Sclerosis. <i>Dickerson, W. W.</i>	683
Neurological Complications of Insulin Shock Therapy with E.E.G. Studies. <i>Halle, L., and Ross, J. F.</i>	703
Babinski Reflex and Marie-Foix Flexor Withdrawal Reflex. <i>Wartenburg, R.</i>	713
*Glucose Tolerance in Chronic Schizophrenia and Senile States. <i>Simon, W., and Garvey, J. T.</i>	717
Postpartum Necrosis of the Adenohypophysis with Hypoglycemic Convulsions. <i>Clark, E. C., et al.</i>	724
E.E.G. Prognosis in Vascular Hemiplegia Rehabilitation. <i>van Buskirk, C., and Zarling, V. R.</i>	732
*Effect of E.C.T. on the Blood Pressure in Psychotic Patients. <i>Igersheimer, W. W., and Stevenson, J. A. F.</i>	740
*Anticonvulsant Drug Therapy of Behavior Problem Children with Abnormal E.E.G. s. <i>Pasamanick, B.</i>	752

Dandy's Striatal Theory of "The Center of Consciousness": Surgical Evidence and Logical Analysis Indicating Its Improbability.

In 1946 Dandy marshalled evidence to support the theory that the cerebral "center of consciousness" is located in the anterior striatum—specifically, in the oral portions of the head of the caudate nucleus and the putamen. He maintained that a lesion of these structures on one or both sides is followed by complete and permanent loss of consciousness.

Of 38 patients with Parkinsonism and 5 with torticollis on whom the author operated within the past decade 27 were subjected to removal, under direct vision, of portions of the anterior striatum corresponding to or exceeding the limits of the "center" described by Dandy. Three of the 27 patients died after operation and necropsy confirmed the existence of the intended lesions. Of the remaining 24 patients the post-operative period of none was characterized by enduring "unconsciousness." In 14 instances the surgical lesions were produced on the right side, in 9 on the left, and in 1, on both sides.

An analysis of the factual data presented by Dandy and the *modus operandi* by which he formulated the anterior striatum theory suggests that (a) in its present form the problem is not scientifically solvable; (b) the clinical material employed was inept for its intended purposes; (c) inferences were commonly mistaken for facts; (d) unwarranted assumptions were frequently made; (e) numerous variables inhering in the problem were overlooked or arbitrarily discounted, and (f) the fallacies of *petitio principii* and *non sequitur* were exercised.

The currently available data render the anterior striatum theory of the "center of consciousness" improbable.

(Author's abstr.)

Glucose Tolerance in Chronic Schizophrenia and Senile States.

Twenty-eight patients with chronic schizophrenia were compared with 10 patients with senile psychosis and studied with a modified Exton-Rose glucose tolerance test.

Of the patients with chronic schizophrenia, 67.9 per cent. showed abnormal, diabetic-like responses, as compared with 80 per cent. of the group with senile psychosis.

The mean values for the two groups reveal a severer disturbance in the senile patients.

It appears that this biochemical disturbance is related not only to stress, tension and anxiety but also to the ageing process. (Authors' abstr.)

Effect of Electroshock on the Blood-pressure in Psychotic Patients.

1. Immediately following the administration of electro-shock to psychotic patients, there are sharp systolic hypertension and diastolic lability. Both the systolic and the diastolic blood pressure return to preshock levels within 10 to 20 minutes. Patients with different psychoses seem to have similar blood-pressure responses.

The atypical blood-pressure responses of a hypertensive psychotic patient are described.

2. The delayed effects on blood pressure produced by the administration of electroshock in normotensive psychotic patients are as follows:

(a) Systolic and diastolic hypotension is present after 6 to 10 electroshocks have been given.

(b) Thereafter both systolic and diastolic blood pressures tend to return to the preshock levels and may not reach them until two weeks after the administration of the last electroshock. This phase is characterized by a widely divergent range of basal blood pressures.

Similar, but more pronounced, effects have been found in five hypertensive psychotic patients.

3. Changes in vascular reactivity in response to the cold pressor test attributable to electroshock treatments have not been observed in psychotic patients.

(Authors' abstr.)

Anticonvulsant Drug Therapy of Behavior Problem Children with Abnormal Electroencephalograms.

Twenty-one boys with behavior problems of varied causations, 6 to 13 years of age, with various electroencephalographic abnormalities, in residential treatment in a children's psychiatric ward, received one or more anticonvulsant drugs, including diphenylhydantoin (dilantin), methylphenylethylhydantoin (mesantoin), trimethadione (tridione) and phenobarbital. Their behavior was noted fairly independently by a number of observers throughout the course of therapy. With minor exceptions the results were almost uniformly disappointing in producing any significant improvement in behavior. An attempt is made to explain the psychodynamics involved in the improvement of behavior disorders under drug administration in out-patient use, and a hypothesis is offered for the rationale of amphetamine therapy in the behavior disorders. (Author's abstr.)

JULY.

Mechanism and Cortical Representation of the Feeding Pattern.	Babkin, B. P., and van Buren, J. M.	1
Occlusion of the Middle Cerebral Artery.	Harvey, J., and Rasmussen, T.	20
Is There a Specific Personality in Tuberculous Patients?	Demuth, E. L.	30
Psychosis Occurring during Antabuse Administration.	Usdin, G. L., and Robinson, K. E.	38
Psychological Studies on Patients with Multiple Sclerosis.	Harrower, M. R., and Kraus, J.	44
Laseque Sign and Kernig Sign.	Wartenberg, R.	58

AUGUST.

- Exfoliative-cell Diagnosis of Central Nervous System Lesions. *Platt, W. R.* 119
 Malignant Tumors in the Institutionalized Psychotic Population. *Schaflen, A. E.* 145
 *Use of Methylphenylsuccinimide in Treatment of *Petit Mal* Epilepsy. *Zimmermann, F. T.* 156
 Effects of the Administration of A.C.T.H. on Patients with Myasthenia Gravis. *Torda, C., and Wolff, H. G.* 163
 *Lesions of Transorbital Lobotomy. *Freeman, W., and Williams, J. M.* 191
 Pneumoencephalographic Study of C.S.F. Absorptive Block Mechanisms. *Aird, R. B., and Zealear, D.* 199

Use of Methylphenylsuccinimide in Treatment of Petit Mal Epilepsy.

The data show that N-methyl-a-phenylsuccinimide (PM 334) is equal to, if not superior to, trimethadione (tridione) in therapeutic efficacy in the group studied and has the advantage of being relatively nontoxic. Animal tests likewise indicate that PM 334 is much more active than trimethadione. In the author's experience, N-methyl-a-phenylsuccinimide has also proved more efficacious in that group of cases in which standard medicaments gave only indifferent to fair results.

Complete control of seizures was obtained for a period of from 4 to 31 weeks, with an average of 12 weeks for the group, in 30 per cent. of the total case-load on an average daily dose of 2.4 gm. Practical control was secured in 30 per cent. of the cases, this group showing an average reduction in attacks of 90 per cent. below the pre-experimental frequency for 13 weeks. Thirty-two per cent. of the total case-load showed an average reduction in attacks of 50 per cent., while only 8 per cent. of the entire group was not helped at all over an average period of seven weeks. (Author's abstr.)

Lesions of Transorbital Lobotomy.

Transorbital lobotomy produces minor lesions of the skull and dura. The cortex is usually traumatized very little. The distinctive lesions are within the white matter, the incision severing the thalamofrontal radiation just lateral to the anterior horn of the lateral ventricle, although sometimes penetrating the ventricle and lacerating the caudate nucleus. There is sometimes a hemorrhagic cavity in the frontal white matter, which evolves into a cyst with pigmented walls. Wallerian degeneration can be traced into the frontal lobe, and also through the internal capsule into the pons. Retrograde degeneration on the thalamus is milder than that seen after prefrontal lobotomy.

From the pathologic standpoint, transorbital lobotomy is a clean-cut, selective operation for severing the thalamofrontal radiation. (Authors' abstr.)

ARCH. PSICOL. NEUR. PSICHIAT.

VOL. XII.

APRIL, 1951.

- The Organization and Function of the Cerebral Cortex. *Bailey, P.* 91
 The Attitude Theory of Emotion. *Bull, N.* 108
 Experimental Research on the Significance of the Test of Toulouse and Piéron. *Kanizsa, G.* 116
 Is the Principal Role and Function of Behavioural Life the Anatomic Functional Development and Organization of the Motor Cortex? *Negri, V.* 134

JUNE.

- The Representation of the Infantile Universe. *Dalla Volta, A.* 163
 The "Bunch of Grapes" Test in Psychiatry. *Sanguineti, J., and Sigurta, R.* 218

ARG. ASSIST. PSICOPAT., SAO PAULO.

VOL. XV.

1950.

- The Meaning of Semiology in Mental Diseases. *Silveira, A.* 5
 Remarks on the Mode of Action of Leucotomy *Yahn, M.* 23

ARG. NEURO-PSIQUIAT.

VOL. IX.

MARCH, 1951.

Observations on Steinert's Disease. <i>Azzi, E.</i>	I
Researches on the Psychodiagnostic of Rorschach on 110 Children with Different Nervous Diseases. <i>Schachter, M.</i>	9
Therapeutic Results in 50 Cases of Neurosyphilis. <i>Canelas, H. M.</i>	21
Kyphoscoliotic Paraplegia. <i>Filho, R. M., et al.</i>	32
Cerebral Cysticercosis. <i>Caetano da Silva, J. A., jun.</i>	43
Schistosomiasis with Spinal Meningo-radicular Lesions. <i>Canelas, H. M., et al.</i>	48
Clinical Sub-divisions of the Schizophrenias. <i>Pires, N., et al.</i>	56

JUNE.

The Treatment of Myasthenic Pseudo-paralysis. <i>Furtado, D., and da Costa, F.</i>	103
Some Considerations of the Treatment of Tetanus. <i>Veronesi, R., and Alves Meira, J.</i>	119
Neurological Complications from Osteomata of the Paranasal Sinuses. <i>Filho, R. M., and Cutin, M.</i>	133

BRAIN.

VOL. LXXIV.

JUNE, 1951.

A Review of the Symptoms and Signs of Acoustic Neurofibromata. <i>Edwards, C. H., and Paterson, J. H.</i>	144
*The Familial Incidence of Disseminated Sclerosis and its Significance. <i>Pratt, R. T. C., et al.</i>	191
*An Experimental Study of the Hippocampal Connexions of the Cingulate Cortex in the Rabbit. <i>Adey, W. R.</i>	233

The Familial Incidence of Disseminated Sclerosis and its Significance.

(1) The slow recognition of a genetic factor in the aetiology of disseminated sclerosis has been due to a number of causes, including the low familial incidence, the lack of published material, and the difficulty in distinguishing the progressive form of disseminated sclerosis from familial spastic ataxia and paraplegia.

(2) 184 families in which more than one case of disseminated sclerosis occurred have been collected from the literature. In this paper a further 33 families are recorded.

(3) In a series of 168 consecutive cases of disseminated sclerosis seen by the authors during a period of eighteen months there were 12 instances of one or more relatives being similarly affected. In an earlier series of 142 patients, in which the inquiry was more limited, the family history was positive on 8 occasions. Therefore in a total of 310 cases the familial incidence was 6.5 per cent. The case histories of affected members of families are recorded.

(4) The incidence of disseminated sclerosis in the sibs of 168 cases and in the parents of 310 cases is shown to be significantly higher than that expected on the basis of a random distribution of the disease.

(5) A few additional pedigrees of particular interest are described, including the occurrence of the disease in a mother and four of her daughters, and an example of the disease occurring by direct transmission in three generations.

(6) The clinical features and relative frequency of certain familial degenerative disorders of the spinal cord and of disseminated sclerosis are compared.

(7) The present study supports the view that a genetic factor is present in disseminated sclerosis, and that there is evidence pointing to both a dominant and a recessive mode of inheritance.

(8) A comparison is made between disseminated sclerosis and some other diseases in which a genetic factor plays a role in the aetiology. It is concluded that the aetiological factor or factors causing disseminated sclerosis may act more readily in the presence of an inherited disposition towards this disease.

(Authors' abstr.)

An Experimental Study of the Hippocampal Connexions of the Cingulate Cortex in the Rabbit.

(1) An experimental study has been made in the rabbit of the connexions of the limbic cortex with the hippocampal region, using the silver staining method of Gleebs to demonstrate degenerating fibres and terminals following cortical ablation.

(2) It has been found that there is a strong connexion from the posterior cingulate and retrosplenial areas to the subiculum and presubiculum. The fibres run as two distinct laminae vertically downwards through the substance of the presubicular and subicular cortex. The superficial weaker lamina is situated in the outermost layer of the cortex. The broader and deeper lamina shows numerous degenerating terminals in the presubicular and subicular cortex.

(3) Following lesions in the posterior cingulate and retrosplenial cortex degenerating fibres can be seen in sagittal sections in the upper part of the presubiculum and the upper part of the dentate gyrus. Their course to the dentate gyrus and presubiculum resembles closely that of the perforating temporo-ammonic tract of Cajal.

(4) A commissural connexion between the posterior cingulate and retrosplenial regions of one side and the corresponding regions of the opposite side has been demonstrated passing through the dorsal part of the splenium of the corpus callosum.

(5) Lesions in the anterior cingulate cortex produced severe degeneration in the cingulum extending posteriorly around the splenium of the corpus callosum to the upper part of the subiculum and presubiculum. Terminal degeneration was seen around the cells of the subiculum and presubiculum.

(6) Terminal degeneration in the posterior cingulate cortex was seen in laminae I and IV following lesions in the anterior cingulate cortex.

(Author's abstr.)

SEPTEMBER.

On the Interpretation of Experimental Studies of Cortical Motor Function.

Walshe, F. M. R. 249

Further Studies of the Effects of Cortisone and A.C.T.H. on Neurological

Disorders. *Shy, G. M., and McEachern, D.* 354

BR. J. ADDICT.

VOL. XLVII.

JULY, 1950.

Modern Techniques for the Treatment of Acute and Prolonged Alcoholism.

Paterson, A. S. 3

Biochemistry and Alcoholism. *MacLeod, L. D.* 21

Alcohol and the Motorist. *Bett, W. R.* 40

Biological Treatment of Chronic Alcoholism by Apomorphine. *de Morsier, G., and Feldman, H.* 50

Some Observations on the Recent Advances in the Treatment of Alcoholism.

Williams, L. 62

BR. J. MED. PSYCHOL.

VOL. XXIV.

1951.

Some Problems of Validation of Projective Techniques. *Ainsworth, M. D.* 151

The Rorschach Test in Obsessional Neurosis with Special Reference to the Effects of Pre-frontal Leucotomy. *McFie, J., et al.* 162

Rorschach Content Analysis. *Sandler, J., and Ackner, B.* 180

A Rorschach Study of Rosacea and Morbid Blushing. *Plesch, E.* 202

The Use of Puppets in Child Psychotherapy. *Hawkey, L.* 206

BR. J. PSYCHOL.

VOL. XLII.

AUGUST, 1951.

Temperamental Differences in Maze Performance. I. *Foulds, G. A.* 209

A Study of Temperament in Adolescence. *Heron, A.* 218

There is no Problem of Meaning. <i>Humphrey, G.</i>	238
Toward the Reinstatement of the Concept of the Self. <i>Litwinski, L.</i>	246
On Some Difficulties Encountered in the Use of Factorial Designs and Analysis of Variance with Psychological Experiments. <i>Smith, B. B.</i>	250
Attention to Change. <i>Berlyne, D. E.</i>	269

BULL. LOS ANGELES NEUR. SOC.

VOL. XVI.

JUNE, 1951.

Epilepsy in Mythology, Legend and Folk-lore. <i>Courville, C. B.</i>	213
Formation and Absorption of Fluid in the Spinal Subarachnoid Space in Man. <i>Boldrey, E. B., et al.</i>	225
Bilateral Lesions of the Anterior Cingulate Gyri. <i>Nielsen, J. M., and Jacobs, J. C.</i>	231
*Anterior Cingulate Gyrus and Corpus Callosum. <i>Nielsen, J. M.</i>	235
Autonomic Phenomenon Noted during Cerebral Angiography. <i>Heifetz, M. D.</i>	251

Anterior Cingulate Gyrus and Corpus Callosum.

(1) Irritative and partly destructive lesions (not section) of the anterior corpus callosum cause a state of emotional excitability, confusion, motor unrest, irritability and often convulsions.

(2) As destruction of the corpus callosum progresses laterally the anterior cingulate gyri are undermined and their projection systems are destroyed.

(3) Undermining of the anterior cingulate gyri in the human subject, when the corpus callosum has been softened, causes complete apathy with akinesia and mutism.

(4) In all probability the anterior cingulate gyri have the same function in the human subject as in the monkey; it is, among other things, the cortical area for emotional expression.

(5) Since all action is emotionally motivated, absence of emotional expression leads to absence of all activity. When the corpus callosum is, in addition, degenerated but not severed the individual has the mechanism of movement interfered with: he has apraxia. (Author's abstr.)

CERVELLO.

VOL. XXVII.

JULY, 1951.

Variations in Acetylcholine in the Brain of Rabbits Following Treatment by Shock, etc. <i>Poloni, A.</i>	241
Isolated Softening in the Dentate Nucleus in Syphilitic Subjects. <i>Della Beffa, A.</i>	257
A Case of Hemiballismus. <i>Fattovich, G.</i>	269
A Study on Heredity in Senile Dementia. <i>Pluchino, G.</i>	293

CONF. NUER.

VOL. XI.

1951.

Iron-pigment in the Brain in Subdural Haemorrhage. <i>Loustalot, P.</i> . . .	193
Congenital Universal Indifference to Pain and Temperature. <i>Moffie, D.</i> . .	219
Electric Stimulation and Therapeutic Coagulation of the Thalamus in Man (Facial Neuralgia). <i>Monnier, M., and Fischer, R.</i>	282
Radiological Research after Transorbital Leucotomy. <i>Fiamberti, A. M.</i> . .	309

DIS. NERV. SYST.

VOL. XII.

JUNE, 1951.

Neurology and the Nervous System of Man. <i>Arieff, A. J.</i>	163
Neuropsychiatry in the Aleutian Islands. <i>Jones, C. H.</i>	172
Insulin Shock Therapy. <i>Mace, N. C., et al.</i>	178
E.C.T. in the Presence of Pulmonary Tuberculosis. <i>Karliner, W., and Savitsky, N.</i>	186

JULY.

Principles and Practice of Neuropsychiatry.	<i>Heldt, T. J.</i>	195
Phenacetylurea in Convulsive Disorders.	<i>Perry, G. F., and Simonds, S.</i>	200
A Training Program for Out-patient Psychotherapy.	<i>Newell, H. W.</i>	206
Alteration of Accessibility with Scopolamine.	<i>Goldner, R. D., and Forrer, G. R.</i>	213

AUGUST.

Epileptic Patients Treated with Aureomycin.	<i>Stamps, F. W., et al.</i>	227
Electroconvulsive Therapy.	<i>Gayle, R. F., and Campbell, R. E.</i>	230
Review of Certain Lobectomy Processes.	<i>Johnson, L. C., and Benjamin, C.</i>	236
Hypnosis and Productive Orientation.	<i>Schneck, J. M.</i>	241
A Statistical Analysis of 400 Sodium Pentothal Interviews of 125 Individual Cases.	<i>Tilkin, L.</i>	243
Diabetic Dorsal Sclerosis of the Spinal Cord.	<i>Bunting, J. J.</i>	245

E.E.G. CLIN. NEUROPHYSIOL.

VOL. III.

MAY, 1951.

The E.E.G. in Cases of Subdural Hematoma and Hydroma.	<i>Sullivan, J. F., et al.</i>	131
E.E.G. Findings in Essential Hypoglycemia.	<i>Ross, I. S., and Loeser, L. H.</i>	141
E.E.G. During a Cycle of Addiction to Keto-temidone Hydrochloride.	<i>Altschul, S., and Wikler, A.</i>	149
Acetylcholine Sensitivity in Diseases of the Motor System with Special Regard to Myasthenia Gravis.	<i>Engboek, L.</i>	155
*Diffuse Thalamic Projection to Cortex.	<i>McLardy, T.</i>	183
Cortical and Subcortical Components in the Recruiting Responses.	<i>Arduini, A., and Terzuolo, C.</i>	189
*Cingulate-cerebellar Mechanisms in the Physiological Pathogenesis of Epilepsy.	<i>Lennox, M. A., and Robinson, F.</i>	197
The Cerebellar Electrogram.	<i>Swank, R. L., and Brendler, S. J.</i>	207
The Effect of Atropine on Cortical Potentials.	<i>Funderbunk, W. H., and Case, T. J.</i>	213
The Effects of Temperature on the Spontaneous and Induced Electrical Activity in the Cerebral Cortex of the Golden Hamster.	<i>Chatfield, P. O., et al.</i>	225
The Slowly Changing Voltage of the Brain and the Electrocorticogram.	<i>Goldensohn, E., et al.</i>	231

Diffuse Thalamic Projection to Cortex: an Anatomical Critique.

A fallacy is pointed out in Morison and Dempsey's claim to have excluded by experiment the possibility that diffuse activation of cortex from the thalamus occurs by way of the specific projection nuclei; they only excluded the primary neurones of sensory relay nuclei. The argument by exclusion that there must be a non-specific projection system from thalamus to cortex therefore no longer holds.

Review of morphological aspects of the intralaminar nuclei and the reticular nucleus, which have been postulated to make up such a diffuse thalamo-cortical projection system, reveals evidence suggesting that none of these nuclei possesses a direct diffuse projection to neocortex. There is, however, circumstantial evidence pointing to the possibility that the "centromedian complex" of intralaminar nuclei diffuses activity within the thalamus, and hence can act as a distributing centre for widespread activation of the cortex by way of the corticopetal connections of some of the specific projection nuclei. The evocation of cortical recruiting responses from the neighbourhood of the smaller rostral and medial intralaminar nuclei may be attributable to activation of nerve-fibres of passage coursing between the centromedian nucleus and regions rostral to the thalamus and between left and right centromedian nucleus.

There are several morphological objections to regarding the reticular nucleus and the centromedian nucleus as two parts of one system. (Author's abstr.)

Cingulate-cerebellar Mechanisms in the Physiological Pathogenesis of Epilepsy.

(1) The effects of electrical stimulation of the anterior cingulate gyrus are described.

(2) Respiratory, motor and electroencephalographic effects are observed and include suppression and facilitation in each category. Respiratory effects consist of arrest and hypernoea. Motor effects consist of arrest of spontaneous motor movement and facilitation in the form of a jerk of the muscles of the face. With increasing intensity of stimulation, the jerking involves progressively the muscles of the neck, forelimbs, trunk and hindlimbs, in that order.

(3) Electroencephalographic suppression has been reported in detail previously. After-discharge may also be produced by stimulation of the anterior cingulate gyrus, but not of the pre- or sub-callosal areas nor of the posterior cingulate gyrus. Optimum parameters of stimulation are: frequency, 30 per second, pulse duration, 11 to 16 msec., and intensity, 2 to 3 volts. The stimulus is applied for 10 seconds and the after-discharge persists 5 to 30 seconds after cessation of stimulation. It usually shows a characteristic 3-per-second spike and wave configuration, although the rate may be 12 to 18 per second. It is transmitted preferentially to the cerebellum, where it may be amplified and at a faster rate. It is seen less often in the lateral cerebral hemispheres, has been recorded from the hippocampal formation, or may remain localized.

(4) Electrical stimulation of the uncus elicits local after-discharge, which spreads preferentially to the temporal tip and posterior orbito-frontal areas, but may involve the anterior cingulate gyrus and cerebellum as well.

(5) Electrical stimulation of the cerebellum does not elicit local or transmitted after-discharge.

(6) Dilantin elevates the threshold of motor cortex to the point of unresponsiveness at maximal stimulation but does not alter the threshold of the anterior cingulate gyrus.

Triodine elevates the threshold of the motor cortex and of anterior cingulate gyrus slightly.

(7) The similarities are reviewed between the effects of stimulation of the anterior cingulate gyrus and the clinical seizures of the *petit mal* triad. It is suggested that *petit mal* triad seizures are attributable to discharge in a system which includes the anterior cingulate gyrus and cerebellum as well as the anterior and mid-line thalamic nuclei.

(8) A functional integration in this system of the hippocampal formation and entorhinal areas afferent to it is suggested.

(Authors' abstr.)

ENCEPH.

VOL. XL.

1951.

Synaesthesias in Mescaline Intoxication.	Delay, J., et al.		I
The Puerperal Psychosis.	Balduzzi, E.		11
A Contribution to the Study of Infantile Sodomy.	Schacter, M., and Cotte, S.		44
The Problem of Hysteria.	Ajuriaguerra, J.		50
An Anatomico-clinical Case of Arsenical Encephalopathy.	de Morsier, C., and Feldman, H.		97
"Daseinanalyse" in Psychiatry.	Binswanger, L.		108
Perception in Mental Disease.	Block, G.		114
Visuo-constructive Disturbances from a Right Parieto-occipital Lesion.	Hecaen, H., et al.		122
The "Jacksonism" of Ribot.	Delay, J.		185
Depersonalization.	Krapf, E-F.		217

EVOL. PSYCHIAT.

VOL. XXIII.

APRIL-JUNE, 1951.

Some Aspects and Medico-legal Problems of Sexual Delinquency.	Caron, M.		192
The Schizophrenic Designer.	Ferdière, G.		215
Clinical and Therapeutic Reflections on Alcoholism.	Fouquet, P.		231
The Centripetal and Centrifugal Currents of the Volitional Life of Epileptics.	Schmidt, P.		263

FOL. PSYCHIAT. NEUR. NEUROCHIR.

VOL. LIV.	JULY, 1951.
Degeneration and Stigmata Degenerationis. <i>Smitt, W. G. S.</i>	175
The Morbid Anatomy of the Heredo-degenerative Affections of the Nervous System. <i>Moyjes, F. E. P.</i>	198
Spino-cerebellar Degeneration. <i>Biermond, A.</i>	216
Clinical Aspects of the Degenerative Diseases of the Cerebro-spinal Motor System. <i>Hoelen, E.</i>	224
Some Remarks on the E.E.G. and its Clinical Use in Neurology. <i>Bartsrta, H. K. G.</i>	254

GENET. PSYCHOL. MONOGR.

VOL. XLIII.	MAY, 1951.
A Psychological Study of Physical Scientists. <i>Roe, A.</i>	121

INTERNAT. J. PSYCHOANAL.

VOL. XXXII.	1951.
Remarks on the Psychoanalysis of Schizophrenia. <i>Eissler, K. R.</i>	139
The Structural Problem in Schizophrenia. <i>Wexler, M.</i>	157
The Structure of Paranoid Ideas. <i>Waelder, R.</i>	167
A Contribution to the Study of the Dream Screen. <i>Rycroft, C.</i>	178
Pathological Generosity. <i>Lewinsky, H.</i>	185
Rumpelstilzkin in the Analytical Situation. <i>Rowley, J. L.</i>	190
Oral Mechanism in Constipation and Diarrhoea. <i>Szaez, T. S.</i>	196

J. AB. SOC. PSYCHOL.

VOL. XLVI.	APRIL, 1951.
Perception of Rorschach Concepts as Related to Personality Deviations. <i>McReynolds, P.</i>	131
Non-adaptive Group Behavior. <i>Mintz, A.</i>	150
Projection of Anxiety Aroused by Sexual Ideation in Mental Hospital Patients. <i>Jacobs, A.</i>	160
Problem Solving Rigidity and Personality Structure. <i>Cowen, E. L., and Thompson, G. G.</i>	165
The Effect of Mental Set and Item Structure upon Response to a Projective Test. <i>Meltzoff, J.</i>	177
Deviation, Rejection and Communication. <i>Schachter, S.</i>	190
The Prognostic Importance of Delusions in Schizophrenia. <i>Albee, G. W.</i>	208
The Mechanism of Hypnotic Age Regression. <i>Orne, M. T.</i>	213
Re-individualizing the Repression Hypothesis. <i>Belmont, L., and Birch, H. G.</i>	226

JULY.

Personal Tempo. <i>Rimoldi, J. A.</i>	283
Perceptual Aspects of Repression. <i>Rosenstock, I. M.</i>	304
Experimental Frustration in a Group Test Situation. <i>McKinney, F., et al.</i>	316
An Exploratory Investigation of Autistic Perception. <i>Smith, K. R., et al.</i>	324
Problem-Solving by Small Groups Using Various Communication Nets. <i>Heise, G. A., and Miller, G. A.</i>	327
Intellectual Performance of Cryptogenic Epileptics, Symptomatic Epileptics and Post-traumatic Encephalopath. <i>Winfield, D. I.</i>	336
Experimental Stress and Alleged Rorschach Indices of Anxiety. <i>Eichler, R. M.</i>	344
Testing for the Existence of Psychometric Patterns. <i>Block, J., et al.</i>	356
A Personality Scale for Dominance. <i>Gough, H. G., et al.</i>	360
The Nature and Meaning of the Rorschach White Space Response. <i>Fonda, C. P.</i>	378
Responses of Psychiatric Patients to Threat of Failure. <i>Miller, D. R.</i>	378
The Discriminatory Recognition of Visual Pattern Under Hypnosis. <i>Weitzenhoffer, A. M.</i>	388

Group Structure and Perception. <i>Bovard, E. W., jun.</i>	398
Competition. <i>Fredericson, E.</i>	406
Intellectual Malfunctioning and Personality. <i>Weisskopf, E. A.</i>	410
Changes in Attitude Through Communication. <i>Hovland, C. I.</i>	424
A Tension Index of Adjustment, etc. <i>Walton, R. E., et al.</i>	438

J. BRAS. PSIQUIAT.

VOL. I.	1951.
"Bio-criminogenesis." <i>Pende, N.</i>	3
The Diagnosis of Dangerous States. <i>Loudet, O.</i>	14
"Psycho-criminogenesis." <i>Lagache, D.</i>	32
Temporal Leucotomy. <i>Yahn, M., et al.</i>	65
The Phenomenology of Schizophrenia. <i>Nobre de Melo, A. L.</i>	74
Clinical Subdivision of the Schizophrenic Group. <i>Langfeldt, G.</i>	141
Hyperpyretotherapy in Schizophrenia. <i>Buscaino, V. M.</i>	154
The Behaviour of 17-Ketosteroids in E.C.T. <i>Alexandre, H., and Ferreira, A. C.</i>	207

J. CLIN. PSYCHOL.

VOL. VII.	JULY, 1951.
On the Disuse and Misuse of P.Q.Qs. and O. Techniques in Clinical Psychology. <i>Cattell, R. B.</i>	203
Research in Clinical Psychology: 1950. <i>Schofield, W.</i>	215
The Prognostic Value of the Metenym Test in a Follow-up Study of Psycho-surgery Patients and their Controls. <i>Zubin, J., and Windle, C.</i>	221
A Study of the Relationship between the Verb-objective Quotient and the Rorschach Experience Balance. <i>Hays, W., et al.</i>	224
The Figure-Background Relationship in Children with Cerebral Palsy. <i>Dolphin, J. E., and Cruickshank, W. M.</i>	228
A Factor Analysis of some Szondi Pictures. <i>Guertin, W. H.</i>	232
Sex Differences in the Rosenzweig P.F. Study, Children's Form. <i>Spache, G.</i>	235
Symbolic Meanings in the Rorschach Cards. <i>Rosen, E.</i>	239
The Relationship between Certain Measureable Functions of Autonomic Nervous System Activity and Color Responses on the Rorschach Test. <i>Hughes, H., et al.</i>	244
A Behaviour Rating Scale Suitable for Use in Mental Hospitals. <i>Lucero, R. J., and Meyer, B. T.</i>	250
An Objective Method of Evaluating Mental Status. <i>Roirell, J. T.</i>	255
An Analysis of the Elgin Prognostic Scale. <i>Lorr, M., et al.</i>	260
The Use of Tolserol in Psychological Testing. <i>Mercer, M., and Hecker, A. O.</i>	263
A Comparison of the Performance of a Randomly Selected College Population on the M.M.P.I. and the P.-S. Experience Blank. <i>Cauffiel, P. W., and Snyder, W. U.</i>	267
The Clinician and his Predictions. <i>Dailey, C. A.</i>	270
Directions for Administration of the Achromatic-Chromatic H-T-P. <i>Buck, J. N.</i>	274
A Tabulation Method for Analysing Combinations of Rorschach Scores. <i>Hammond, K. R.</i>	276
Use of the Blacky Pictures with a Child whose Oedipal Desires are Close to Consciousness. <i>Michal-Smith, H., et al.</i>	280
The Application of Hypnosis to Nondirective Psychotherapy. <i>Kline, M. V.</i>	283
A Note on Extended Findings with the M.M.P.I. in Predicting Response to E.C.T. <i>Pearson, J. S., and Sirenson, W. M.</i>	288
Norms for Scatter Analysis on the Weschler Intelligence Scale. <i>Alimena, B.</i>	289

J. COMP. NEUR.

VOL. XCIV.	JUNE, 1951.
Influence of the Forebrain on Somato-motor Activity. I and II. <i>Hodes, R., et al.</i>	381 and 409
Extrapyramidal Nuclei Among Mammals. <i>von Bonin, G., and Shariff, G. A.</i>	427

- The Course of the Fibres Arising from the Nucleus Gracilis and Cuneatus of the Cat. *Matzke, H. A.* 439
- Nucleolar Changes and Development of Nissl Substance in the Cerebral Cortex of Fetal Guinea Pigs. *La Velle, A.* 453
- A Note on Nodes of Ranvier in the C.N.S. *Bodian, D.* 475
- The Effect of Neuro- and Adreno-hypophysectomy on Retrograde Degeneration in Hypothalamic Nuclei of the Rat. *Bodian, D., and Maren, T. H.* 485

J. COMP. PHYSIOL. PSYCHOL.

VOL. XLIV.

JUNE, 1951.

- Response Potential as a Function of Effort. *Applezweig, M. H.* 225
- True, Sham and Esophageal Feeding as Reinforcements. *Hull, C. L., et al.* . . 236
- Studies in Secondary Reinforcement. II. *Hall, J. F.* 246
- A Study in Place and Response Learning as a Discrimination Behavior. *Webb, W. B.* 263
- The Role of Response and Place Learning under Alternating Hunger and Thirst Drives. *McCutchom, K., et al.* 269
- Simple Reaction Chains and their Integration. IV. *Arnold, W. J.* 276
- Performance of Normal and Operated Monkeys on Visual Learning Tests. *Riopelle, A. J., et al.* 283
- Effects of Cortical Lesions upon the Hoarding Behavior in Rats. *Zubeck, J. P.* 310
- The Effects of Large Cortical Lesions on the Solution of Oddity Problems by Monkeys. *Harlow, H. F., et al.* 320
- Sound-induced Seizure in Rats Fed on Amino-acid Deficient Diet. *Bevan, Wm., jun., et al.* 327

AUGUST.

- Studies in Somethesis. I. *Zubek, J. P.* 339
- Emotionality and Audiogenic Seizure Susceptibility in Five Inbred Strains of Mice. *Lindzay, G.* 389

J. EX. PSYCHOL.

VOL. XLI.

MARCH, 1951.

- A Study of Some Relations among Aperiodic Reinforcement, Discrimination Training and Secondary Reinforcement. *Notterman, J. M.* 161
- The Effect of Practice on the Perception of Obstacles by the Blind. *Worchel, P., and Mauney, J.* 170
- The Growth and Decay of Reactive Inhibition as Measured by Alternation Behavior. *Zeaman, W., and House, B. J.* 177
- Effects of Pre-practice Activities on Rotary Pursuit Performance. *Ammons, R. B.* 187
- A Comparison of Transfer Effects during Acquisition and Extinction of Two Instrumental Responses. *Liberman, A. M.* 192
- Similarity in Stimulating Conditions as a Variable in Retroactive Inhibition. *Bilodeau, I. McD., and Schlosberg, H.* 199
- The Effect of an Extra Stimulus upon Strength of Response during Acquisition and Extinction. *Winnick, W. A., and Hunt, J. McV.* 205
- Resistance to Extinction and the Pattern of Reinforcement. II and III. *Haki, H. W., and Grant, D. A.* 216 and 221
- Combined Drives in Learning. *Rethlingshafer, D., et al.* 226

APRIL.

- Secondary Reinforcement of a Simple Discrimination in Human Beings. *Hubbard, W. R.* 233
- Recovery from Retention Loss as a Function of Amount of Pre-recall Warming-up. *Irion, A. L., and Wham, D. S.* 242
- Facilitation and Interference in Performance on the Modified Mashburn Apparatus. I. *Lewis, D., et al.* 247

Temporal Gradients of Response Strength with Two Levels of Motivation.	
<i>Rosenbaum, G.</i>	261
The Effects of Differential Rewards on Discrimination Reversal Learning by Monkeys.	
<i>Meyer, D. R.</i>	268
The Effect of Practice with Brief-exposure Techniques upon Central and Peripheral Visual Acuity, and a Search for a Brief Test of Peripheral Acuity.	
<i>Bruce, R. H., and Low, F. N.</i>	275
Probability Learning and a Negative Recency Effect in the Serial Anticipation of Alternative Symbols.	
<i>Jarvick, M. E.</i>	291
The Effect of Scale Numbering on Scale-Reading Accuracy and Speed.	
<i>Barber, J. L., and Garner, W. R.</i>	298
The Accuracy of Counting Repeated Short Tones.	
<i>Garner, W. R.</i>	310
Conditioned Fear as Revealed by Magnitude of Startle Response to an Auditory Stimulus.	
<i>Brown, J. S., et al.</i>	317
The Intelligibility of Speech as a Function of the Context of the Test Materials.	
<i>Miller, G. A., et al.</i>	329
Conditioning Imagery.	
<i>Leuba, C., and Dunlop, R.</i>	352

J. GEN. PSYCHOL.

VOL. XLIV.

APRIL, 1951.

An Analysis of the Achievements in Spaced and Massed Practice.	
<i>Tsao, J. C.</i>	189
Linguistic Behaviors. I.	
<i>Herman, D. T.</i>	199
Ontogenetic Evidence of a Correlation between the Form and Frequency of Use of Words.	
<i>Baker, S. J.</i>	235
The Application of Zipf's Analysis of Language to Sequences of Restricted Associative Responses.	
<i>Bousfield, W. A., and Barclay, W. D.</i>	253
A Factorial Approach to Rorschach Interpretation.	
<i>Adcock, C. J.</i>	261
Linguistic Behaviors. II.	
<i>Herman, D. T.</i>	273
Hypnoanalysis, Hypnotherapy and Card 12M of the T.A.T.	
<i>Schneek, J. M.</i>	293

J. GENET. PSYCHOL.

VOL. LXXVIII.

JUNE, 1951.

A Study of the Friendship Fluctuations of Pre-adolescents.	
<i>J. E., and Barker, M. E.</i>	131
The Intelligence of Epileptics.	
<i>Read, H. B.</i>	145
Preferences for Rectangular Proportions in College Students and the Aged.	
<i>Nieusiedt, C. W., jun., and Ross, S.</i>	153
Senescence and the Emotions.	
<i>Banham, K. M.</i>	175
The Relationship Between Pubertal Status and Leadership in Junior High School Boys.	
<i>Latham, A. J.</i>	185
Hypnosis and Age Regression.	
<i>Kline, M. V.</i>	195
A Measure of Mental Masculinity and Femininity in Relation to Hypnotic Age Progression.	
<i>Kline, M. V.</i>	207
Identifying the Insecure Child: The Wolff Security Test.	
<i>Martin, W. E.</i>	217

J. NERV. MENT. DIS.

VOL. CXIII.

JUNE, 1951.

On Certain Aspects of the Sensory Organization of the Human Brain.	
<i>Cohn, R.</i>	471
Basal E.E.G.	
<i>Arellano, A. P., and Maclean, P. D.</i>	485
The Psychopathology of Acromegaly.	
<i>Bleuler, M.</i>	497
Experimental Investigation of the Body-mind Continuum in Affective States.	
<i>Pasquarelli, B., and Bull, N.</i>	512
*Ictal and Non-Ictal Psychiatric Disorders in Temporal Lobe Epilepsy.	
<i>Gibbs, F. A.</i>	522
*Chemical Analysis of Spectrophotometric Findings in the C.S.F.	
<i>Spiegel-Adolf, M., et al.</i>	529
Blood Lymphocytes and Adrenal Function in E.C.T. of Psychoses.	
<i>Michael, S. T., and Brown, W. T.</i>	538

Ictal and Non-Ictal Psychiatric Disorders in Temporal Lobe Epilepsy.

Analysis of 458 cases with electroencephalographic evidence of focal seizure discharges reveals that the anterior temporal region is more vulnerable than any other area to the type of injury which results in focal discharging lesions. Ninety-five per cent. of 163 cases with focal seizure activity in the anterior temporal lobe had clinical psychomotor seizures. This is eight times as great as the association between psychomotor seizures and epileptic foci in other parts of the cortex. Psychiatric disorder was more than three times commoner in cases with focal seizure activity in the temporal lobe than in cases with a focus in any other cortical area. The epileptic and psychiatric components of psychomotor epilepsy are independent, and though physiologically antithetic they are anatomically associated. Non-ictal psychiatric disorder is not temporally associated with electroencephalographic abnormalities, but the seizure discharge provides a clue to the anatomic locus of the psychiatric disorder.

The present data suggest that the temporal lobe subserves a hierarchy of neuronal functions. These are divisible into (a) sensation, (b) perception, (c) evaluation, and (d) judgment. The middle and posterior temporal cortex are chiefly concerned with (a) and (b) and the anterior temporal region with (c) and (d). Specific psychiatric symptomatology depends on the type of disorder, minor differences in locus and degree of involvement of specific neurones. Mis-evaluations resulting from disorder in posterior temporal regions result in distortions of the meaning of specific afference streams; for example, hallucinations, micropsia, *déjà vu*. Misinterpretations of the total afferent stream (experience) results in such symptoms as depression and psychopathy. (Author's abstr.)

Chemical Analysis of Spectrophotometric Findings in the Cerebrospinal Fluid.

(1) Ultraspectrophotometry and chemical determination of the ascorbic acid content of the cerebrospinal fluid were carried out simultaneously in 40 cases.

(2) In a part of the material the ascorbic acid and protein content of the C.S.F. accounted for its selective absorption with the peak at 2650 Å. These were cases without definite structural alterations of the central nervous system or with preponderant lesions of the white matter, cases studied one or more years after cerebral injury or in the early stage of an affection of the cerebrum.

(3) In certain pathologic cases (particularly tumors, some convulsive disorders, recent cerebral concussion) a definite difference was found between the selective absorption of the C.S.F. at 2650 Å and the sum of the extinction coefficients corresponding to the ascorbic acid and to the protein content.

(4) Reasons are given supporting the view that this difference is due to the appearance of purine or pyrimidine compounds in the C.S.F.

(Authors' abstr.)

JULY.

Autonomic Changes Paralleling Psychologic Changes in Mentally Ill Patients.

<i>Frumkenstein, D. H., et al.</i>	1
Heroin Addiction in Adolescent Boys. <i>Zimmering, P., et al.</i>	19
Primary Pontile Hemorrhage. <i>Steegmann, A. T.</i>	35
The Recognition and Acceptance of Mood in Music by Psychotic Patients. <i>Simon, B., et al.</i>	66

AUGUST.

Application of a Sociometric Technique to the Study of Lobotomized Patients.

<i>Bockoven, J. S., and Hyde, R. W.</i>	95
Evaluation of the "Draw a Person" Test (Modified) in Thalamotomy with Particular Reference to the Body Image. <i>Freed, H., and Pastor, J. T.</i>	106
Mind, Brain and Psychoneurosis. <i>Taft, A. E.</i>	121
The Syndrome of Sensorimotor Induction in Combined Cerebellar and Labyrinthine Injury. <i>Halpern, L.</i>	137
*Electroshock Therapy in Schizophrenia. <i>Palmer, D. M., et al.</i>	162

Electroshock Therapy in Schizophrenia: a Statistical Survey of 455 Cases.

Four hundred and fifty-five male veteran schizophrenics were treated with a single series of electroshock treatment with the following results:

(1) One hundred and ninety-eight patients or 43.5 per cent. showed either marked or moderate improvement.

(2) Seventy of these 198 relapsed before they could be discharged.

(3) One hundred and twenty-eight patients were discharged with marked or moderate improvement following electroshock. This was a discharge rate of 28.1 per cent.

(4) Forty-eight of the 128 discharges (or 37.5 per cent.) had relapses after they left the hospital, leaving the number of discharges, after a period ranging from 42 to five months, at 80 (or 17.6 per cent.) remaining discharged.

(5) There was a definite relationship between length of illness and remission following shock. Those who remained discharged had a mean illness period of 15 months, while those who remained hospitalized had been ill slightly over 39 months (mean value).

(6) Hebephrenics appeared to respond somewhat less favorably than catatonics.

(7) Those who responded well to electroshock were significantly younger in age than those who did not improve, but further analysis showed that the patients who responded satisfactorily had been ill a shorter period and that illness duration, and not age, was the important prognostic factor.

(8) Whites responded more favorably than negroes, both in terms of hospital discharge and in not suffering relapse after leaving the hospital.

(Authors' abstr.)

J. NEUR. NEUROSURG. PSYCHIAT.

VOL. XIV.

MAY, 1951.

Subacute Cortical Cerebellar Degeneration and its Relation to Carcinoma.

Brain, W. R., et al. 59

The Clinical Features and Response to Cortisone of Menopausal Muscular

Dystrophy. *Shy, G. M., and McEachern, D.* 101

The Surgical Treatment of Extrapyrarnidal Diseases. *Bucy, P. C.* 108

*Electrical Activity of the Human Brain During Artificial Sleep. II. *Wyke,*

B. D. 137

Electrical Activity of the Human Brain During Artificial Sleep.

The cyclical changes induced in each of the major subdivisions of the human brain surface by progressive barbiturate sedation are described.

Evidence is presented to show that during the onset of sleep the brain does not respond in an overall uniform fashion.

It is suggested that while in the waking human brain different cortical areas do not usually possess well-defined electrical identities, during the onset of sleep they pass through a period when they may assume more or less independent patterns of electrical behaviour, the pattern of electrical activity at each stage of sleep being characteristic of the particular region.

(Authors' abstr.)

VOL. XIV.

AUGUST, 1951.

Sensory Disturbances in Cortical Wounds with Special Reference to Pain.

Marshall, J. 187

Confirmation of the Rosenow Antibody-Antigen Skin Reaction In idiopathic Epilepsy. *Bering, E. A., jun.* 205

Local Sign in Autonomic Responses. *Elithorn, A., et al.* 209

Subacute Necrotizing Encephalomyelopathy in an Infant. *Leigh, D.* 216

The Use of Marchi Staining in the Later Stages of Human Tract Degeneration.

Smith, M. C. 222

Neuroticism and Emotional Instability in High-Grade Male Defectives.

O'Connor, N. 226

XCVIII.

148

J. NEUROPATH. EX. NEUR.

VOL. X.

JULY, 1951.

- Neurotoxicity of the 8-Aminoquinolines. III. *Schmidt, I. G., and L. H.* . . . 231
- Observations on Cerebral Arteriosclerosis. *Eros, G.* . . . 257
- Vascular Changes in the Brain in a Fatality Following Electroshock. *Liban, E., et al.* . . . 309
- Distribution of Chromidia in the Sympathetic Ganglion Cells in Man and Dogs with Hypertension. *Nedzel, A. J.* . . . 319
- Histophysiological Effects of Arsenic and its Derivatives on the Central Nervous System. *Grzycki, S., and Kobusowna, B.* . . . 325

J. NEUROPHYSIOL.

VOL. XIV.

JULY, 1951.

- Observations on the Physiological Action of Strychnine. *Wall, P. D., and Horwitz, N. H.* . . . 257
- Relation of Air Exposure of Cortex to Spreading Depression of Leão. *Marshall, W. H., and Essig, C. F.* . . . 265
- Experimentally Derived Correlates Between E.C.G. and Steady Cortical Potential. *Goldring, S., and O'Leary, J. L.* . . . 275
- Electrophysiological Studies of Subcortical Connections of Anterior Temporal Region in Cat. *Stoll, J., et al.* . . . 305
- Vasomotor, Cellular and Functional Changes Produced in Kidney by Brain Stimulation. *Hoff, E. C., et al.* . . . 317

VOL. XIV.

SEPTEMBER, 1951.

- Effects Induced in a Monosynaptic Reflex Path by its Activation. *Eccles, J. C., and Rall, W.* . . . 353
- Action Potentials of Cold Fibres and Intracutaneous Temperature Gradient. *Hensel, H., and Zotterman, Y.* . . . 377
- Effects of Adenine Compounds on Electrocortical Activity. *Robinson, F., and Hughes, R. A.* . . . 387
- The Nucleus Cervicalis Lateralis. *Rexed, B., and Brodal, A.* . . . 399
- Microelectrode Studies of Neural Auditory Activity in Cat. II. *Gross, N. B., and Thurlow, W. R.* . . . 409
- Electrophysiological Measurements of Depth of Thermoreceptors. *Hensel, H., et al.* . . . 423

J. NEUROSURG.

VOL. VIII.

JULY, 1951.

- Prefrontal Lobotomy for the Relief of Pain. *Grantham, E. G.* . . . 405

J. PERSONAL.

VOL. XIX.

MARCH, 1951.

- A Quantitative Study of Perception and Association in Experimental Semi-Starvation. *Brožek, J., et al.* . . . 245
- Perceptual and Asthetic Aspects of the Movement Response. *Arnheim, R.* . . . 265
- Some Implications for T.A.T. Interpretation Arising from Need and Perception Experiments. *Eriksen, C. W.* . . . 282
- Perceptual Attitudes toward Instability. I. *Klein, G. S., and Schlesinger, H. J.* . . . 289
- An Investigation of the Relationship between Intolerance of Ambiguity and Ethnocentrism. *Block, J., and J.* . . . 303
- Masculine Inadequacy and Compensatory Development of Physique. *Harlow, R. G.* . . . 312
- Rate of Learning as a Function of Ego-Alien Material. *Williams, M.* . . . 324
- The Effect of Probability, Desirability and "Privilege" on the Stated Expectations of Children. *Marks, R. W.* . . . 332

J. PROJ. TECHNIQUES.

VOL. XV.

JUNE, 1951.

- Personality Factors in Patients with Duodenal Ulcer. *Poser, E. G.* . . . 131
- Notes on Rorschach Tests of 500 Juvenile Delinquents and a Control Group of 500 Non-delinquent Adolescents. *Schachtel, E. G.* . . . 144
- The Use of Color in the T.A.T. *Thompson, C. E., and Bachrach, A. J.* . . . 173
- A "Story Completion" for Use with the Physically Handicapped. *Freding, B. B.* . . . 299
- Current Problems in Rorschach Theory and Technique. *Hertz, M. R.* . . . 307

J. PSYCHOL.

VOL. XXXII.

JULY, 1951.

- Visual Space and Physical Space. *Groosfeld, H. D.* . . . 25
- The Reliability of the Verhoef Test of Depth Perception. *Trumbull, R.* . . . 35
- An Objective Test of Visual Retention Capacity. *Cohen, J. S., et al.* . . . 43
- Criminal Aliases. *Hartman, A. A.* . . . 49
- Brightness Enhancement in Relation to Target Intensity. *Bartley, S. H.* . . . 57
- An Electromyographic Technique for Recording the Startle Pattern. *Jones, F. P., and Kennedy, J. L.* . . . 63
- Organismic versus Cerebral Localization of Biological Defects in Feeble-mindedness. *Bucklew, J., and Hafner, A. J.* . . . 69
- Fatal Convulsive Seizures in the D.B.A. Mouse Strain. *Vicari, V. M.* . . . 79
- A Factorial Study of Cultural Patterns in the U.S. *Hofstaetter, P. R.* . . . 99

J. SOC. PSYCHOL.

VOL. XXXIII.

MAY, 1951.

- Preface to a Psychology of Sexual Attachment. *Grant, V. W.* . . . 187
- Nationalistic Aspects of the Grimm Brothers' Fairy Tales. *Snyder, L. L.* . . . 209
- Studies of Social Intolerance. I-IV. *Gough, H. G.* . . . 237
- Autocratic versus Democratic Beliefs and Practices of Graduate Nurses. *Nahm, H.* . . . 271
- Censorship and the Kimsey Report. *Ramsey, G. V., and Varley, M.* . . . 279

MIND.

VOL. LX.

JULY, 1951.

- Mr. Kneale on Probability and Induction. I. *Anscombe, F. J.* . . . 299
- Probability and Induction. II. *Kneale, W.* . . . 310
- The Dreariness of Aesthetics. *Passmore, J. A.* . . . 318
- The Argument from Analogy and our Knowledge of other Minds. *Thomson, J. F.* . . . 336
- The Analysis of Conditional Sentences. *O'Connor, D. J.* . . . 351
- The Logic of Causal Propositions. *Burks, A. W.* . . . 363
- Maxims. *Gellner, E.* . . . 383
- A Problem of Lewis Carroll. *Russell, L. J.* . . . 394

NEUROPSYCHIAT.

VOL. I.

SEPTEMBER-DECEMBER, 1950.

- The Classification of Mental Patients. *Carrillo, R.* . . . 337

PISANI.

VOL. LXIV.

SEPTEMBER-DECEMBER, 1950.

- Progress and Lack of Progress of Legal Measures for the Treatment and Prophylaxis of Mental Illness. *Santangelo, G.* . . . 5
- New Work on the Development of Gestalt. *Canziani, G.* . . . 23
- The "Test of Reconstitution" of Buyse. *Riccobono, L.* . . . 43
- A Transorbital Leucotomy with Fatal Result. *Madonia, P.* . . . 63
- Examination under Narcosis in Psychiatry. *Rivas, M.* . . . 77

VOL. LXV.

JANUARY-APRIL, 1951.

Mental Tests in Normal Psychology, in Normal Psychotechnics and in Psychopathology. <i>Migliorino, G.</i>	15
Consideration on Survival in a Case of Schizophrenia Roused after 104 Hours in Insulin Coma. <i>Lupo, V.</i>	39

PROC. ROY. SOC. MED.

VOL. XLIV.

JULY, 1951.

Discussion on Headaches	541
-------------------------	-----

PSYCHIAT.

VOL. XIV.

MAY, 1951.

Knowledge, Morality and Destiny. <i>Huxley, Julian</i>	127
Hysterical Manifestations in Schizophrenic Illnesses. <i>Noble, D.</i>	153
Two Adolescents. <i>Riesman, D.</i>	161
Political Involvement and Interpersonal Relations. <i>Coser, R. L.</i>	213
A Study of Need-fulfillment on a Mental Hospital Ward. <i>Schwartz, C. G., et al.</i>	223

PSYCHIAT. QUART.

VOL. XXV.

APRIL, 1951.

The Future Organization of Psychiatric Care. <i>Lemkau, P. V.</i>	201
Some Physiologic Common Denominators of Histamine, Sex Steroids, Insulin and E.C.T. <i>Sackler, M. D., et al.</i>	213
Psychiatric Aspects of Asthma. <i>Prout, C. T.</i>	237
*Thalamo-cingulate Fasciculotomy. <i>Siris, J. H.</i>	251
The Fiction of the Death Instinct. <i>Levin, A. J.</i>	257
The Relation of Rh to Mental Deficiency. <i>Glasser, F. B., et al.</i>	282
The Emotional Reactions of a Schizophrenic Patient to Shock Therapy. <i>Hayward, M. L.</i>	288
Schizophrenic Reactions during Childhood in Mental Defectives. <i>Bergman, M., et al.</i>	294

Thalamo-cingulate Fasciculotomy.

Occasional undesirable sequelae following psychosurgery indicate the need for a less extensive procedure which may accomplish its purpose without the complication of post-operative personality impairment or epilepsy.

An effort is being made to accomplish this by interruption of the thalamo-cingulate projection because of the evidence of its relationship to emotion, and the fact that the procedure spares a substantial part of the anterior thalamic radiation.

A simple procedure has been described, which seems capable of interrupting these impulses, through a small incision at an easily identified landmark.

(Author's abstr.)

PSYCHOANAL. QUART.

VOL. XV.

APRIL, 1951.

Simulated Pregnancy in a Male. <i>Evans, W. N.</i>	165
Anxiety, Trauma and Shock. <i>Stern, M. M.</i>	179
Illusions, Naïve or Controlled. <i>Sperling, O. E.</i>	204
Psychoanalysis and Brief Psychotherapy. <i>Stone, L.</i>	215
The Character of Jean Jacques Rousseau. <i>Kligerman, C.</i>	237
Some Psychodynamic Reflections upon the Life and Writings of Solon. <i>Engle, B., and French, T. M.</i>	253
Automatic Resistances in Word Association Tests. <i>Baker, S. J.</i>	275
The Inability to Remember Dreams and Jokes. <i>Grotjahn, M.</i>	284

PSYCHOL. REV.

VOL. LVIII.

JULY, 1951.

Intervening Variable or Hypothetical Construct. <i>Marx, M. H.</i>	235
Interruption and Learning. <i>Bogaslavsky, G. W.</i>	248

Word Frequency, Personal Values and Visual Duration Thresholds. <i>Solomon, R. L., and Howes, D. H.</i>	256
Personal Values, Visual Recognition and Recall. <i>Postman, L., and Schneider, B. H.</i>	271
The Constancies in Perceptual Theory. <i>Ittelson, W. H.</i>	285
Theoretical Psychology, 1950. <i>Koch, S.</i>	295
On a Stimulus-Response Analysis of Insight in Psychotherapy. <i>Seeman, W.</i>	302

PSYCHOSOM. MED.

VOL. XIII.

MAY-JUNE, 1951.

Life Situations, Emotions and the Course of Patients with Arterial Hypertension. <i>Reiser, M. F., et al.</i>	133
Relationship Therapy in Essential Hypertension. <i>Shapiro, A. P., et al.</i>	140
Psychologic Mechanisms in Malignant Hypertension. <i>Reiser, M. F., et al.</i>	147
Studies in Diabetes Mellitus: III. <i>Hinkle, L. E., jun., et al.</i>	160
Studies in Diabetes Mellitus: IV. <i>Hinkle, L. E., jun., et al.</i>	184

JULY-AUGUST.

Pseudohermaphroditism. <i>Chapman, A. H., et al.</i>	212
A Preliminary Report on the Role of Emotional Factors in Idiopathic Celiac Disease. <i>Prugh, D. G.</i>	220
Evaluation of a New Psychiatric Screening Test. <i>Saslow, G., et al.</i>	242
Symbolism and Organ Choice in Conversion Reactions. <i>Seitz, P. F. D.</i>	254
A Method for Isolating Presumptive Personality Profiles from Changes in Skin Conductivity During Word Association Tests. <i>Hsü, E. H.</i>	260

Q. J. EX. PSYCHOL.

VOL. III.

AUGUST, 1951.

Changes with Age and with Exclusion of Vision in Performance at an Aiming Task. <i>Szafran, J.</i>	III
--	-----

Q. J. STUD. ALC.

VOL. XII.

JUNE, 1951.

*The Inhalation of Ethyl Alcohol by Man. <i>Lester, D., and Greenberg, L. A.</i>	167
The Failure of Oxygen, Oxygen-Carbon Dioxide or Pyruvate to Alter Alcohol Metabolism. <i>Kinard, F. W., et al.</i>	179
*Psychiatric Implications of the Treatment of Alcoholism with Antabuse. <i>Gottesfeld, B. H., et al.</i>	184
*Psychotic Phenomena Provoked by Antabuse. <i>Martensen-Larsen, O.</i>	206
Alcoholism as a Sickness. <i>Wexberg, L. E.</i>	217
Alcoholism and Social Stability. <i>Straus, R., and Bacon, S. D.</i>	231
*Tolserol in the Treatment of the Postalcoholic State. <i>Herman, M., and Effron, A. S.</i>	261
*A Psychometric Examination of Latent Homosexuality in Alcoholism. <i>Botwinick, J., and Machover, S.</i>	268
Group Therapy in Alcoholism. <i>McCarthy, R. G.</i>	273

The Inhalation of Ethyl Alcohol by Man: I. Industrial Hygiene and Medicolegal Aspects. II. Individuals Treated with Tetraethylthiuram Disulfide.

1. A search of the literature pertaining to the inhalation of alcohol by man indicated that the presently accepted value for the maximum allowable concentration in the air was based on vague qualitative observations, and that it was erroneous from the standpoint of industrial safety and hygiene and of no value for medicolegal purposes.

2. Qualitative observations were made of the effects of varying concentrations of alcohol in the air at various rates of ventilation. It is concluded that concentrations greater than 40 mgm. per litre are intolerably irritating, while at concentrations between 10 and 20 mgm. per liter work might be carried on, albeit not in comfort.

3. Determinations of the percentage of alcohol absorbed from the inspired air showed that 62 per cent. of the alcohol is absorbed.

4. Human subjects were exposed to various concentrations of alcohol in air for periods up to 6 hours, at various rates of ventilation. Determinations of the resulting concentrations of alcohol in the blood indicated a simple relationship for calculating the maximum allowable concentration under various conditions of work. A maximum allowable concentration of 7 mgm. per liter is proposed, which is about 4 times the accepted value.

5. It was shown that intoxication can result from the inhalation of alcohol under certain conditions, and an expression has been given for calculating the concentration which may be expected to develop in the blood provided four facts are known: the concentration of alcohol in the air, the rate of ventilation of the individual, the individual's weight, and the duration of the exposure.

6. Observations on patients under treatment with tetraethylthiuram disulfide showed that the maximum safe concentration for T.E.T.D.-treated individuals is 2 mgm. of alcohol per liter of air. (Authors' abstr.)

Psychiatric Implications of the Treatment of Alcoholism with Tetraethylthiuram Disulfide.

1. In a series of 42 patients treated with tetraethylthiuram disulfide, 8 developed psychotic episodes. Five of these episodes were transitory and responded promptly to the withdrawal of T.E.T.D. and the use of mild sedation. Three were relatively prolonged.

2. The projective, hostile individual who feels threatened by help and who has difficulty in forming interpersonal relationships is usually not a desirable candidate for treatment with T.E.T.D.

3. A history of psychotic episodes, or an indication of incipient psychosis, contraindicates treatment with T.E.T.D.

4. Borderline schizophrenic adjustments, as well as character neuroses with transitional schizophrenic components that may be easily overlooked, should be particularly watched for. In the authors' present series the psychotic reactions developed in these two groups of patients. It is possible, of course, that an unidentified element of selection in the authors' series may differentiate it from other reported groups.

5. Individuals who show a capacity to develop sustained interpersonal relationships and who show some utilizable dependency traits appear to be suitable candidates for treatment with T.E.T.D. The incidence of therapeutic success is highest when T.E.T.D. treatment is employed with individuals selected on the basis of psychiatric criteria of suitability, including a demonstrated ability to utilize psychotherapy. The implications of T.E.T.D. are almost always linked inseparably with the implications of psychotherapy.

6. Five of the eight psychotic responses in the authors' series occurred several weeks after the patient's discharge from the hospital, and indications of mounting anxiety usually had been observable during the earlier T.E.T.D.-alcohol reaction tests. This anxiety, together with parallel signs, can be used in helping to foresee and to handle complications that may arise in the future use of T.E.T.D. Of the three other breakdowns, one emerged shortly after the third T.E.T.D.-alcohol test in the hospital (4 weeks after the beginning of T.E.T.D. medication), one occurred at the first T.E.T.D.-alcohol test, and the third was manifested prodromally during the first test. These findings, along with other considerations, suggest that psychodynamic factors may be responsible. At this stage in the authors' investigation they have been unable to rule out completely possible physiological components that might have contributed to the production of emotional manifestations. Considerable further psychiatric, medical and physiological studies will be necessary before a final evaluation and correlation of these factors can be made.

(Authors' abstr.)

Psychotic Phenomena Provoked by Tetraethylthiuram Disulfide.

Tetraethylthiuram disulfide may give rise to specific psychotic phenomena when taken in doses unnecessarily high for the individual patient.

This can be avoided by continuous observation of the patient for the special, relatively mild, side effects precursory to the state of psychosis. Even in patients

highly sensitive to T.E.T.D. a carefully adjusted minimal dosage may prove to be of therapeutic value. (Authors' abstr.)

Tolserol in the Treatment of the Post-alcoholic State.

Tolserol in doses of 2 to 2.5 gm. per day is of decided benefit in the management of the post-alcoholic state. It markedly reduces or eliminates tremulousness and gastrointestinal symptoms, and improves the subjective state of the patient. It has a lesser effect on sleep. This rapid improvement in the post-alcoholic state facilitates better psychotherapeutic management and reduces the necessity for prolonged hospitalization. (Authors' abstr.)

A Psychometric Examination of Latent Homosexuality in Alcoholism.

1. The purpose of this study was to examine by means of interest tests the hypothesis that regards alcoholism as a condition involving some homosexual component.

2. The M-F and "I" scales of the Terman and Miles Attitude Interest Analysis Test and a mimeographed version of the M-F Scale of the Minnesota Multiphasic Personality Inventory were administered to 39 patients in the alcoholic ward of the King's County Hospital. These scales were given to the same patients in 31 cases.

3. The mean M-F scores were not statistically different from the means of the normative populations employed in the standardization of the tests. There was, however, a significant difference between the "I" score means. These differences point to the "normality" of the experimental alcoholic population in regard to sexual interest pattern.

4. It is concluded that in so far as the tests used in this study measure homosexuality, latent or otherwise, homosexuality cannot be an essential factor in alcoholism, although it may play a dynamic role in individual cases.

(Authors' abstr.)

RASS. STUD. PSICHIAT.

VOL. XL.

1951.

"Lumbar-pubic Electroshock" in Neuropsychiatry. <i>Rebassini, A., et al.</i>	371
Some Cases of Sturge-Weber Disease. <i>Eugenio, C.</i>	379
Narcoanalysis. <i>Bleger, J.</i>	397

REV. NEUROL.

VOL. LXXXIV

MARCH, 1951.

Herpetic Encephalitis of the Newborn. <i>Wildi, E.</i>	201
An Anatomico-pathological Study of Pieces of Brain Removed During Topectomy in Ten Schizophrenics. <i>Messing, H., et al.</i>	230

APRIL.

The Pericommissural Nucleus of the Anterior White Commissure. <i>Grattarola, F. R.</i>	273
--	-----

REV. NEURO-PSIQUIAT.

VOL. XIII.

SEPTEMBER, 1950.

Seventy-two Cases of Cysticercosis in the Institute of Neurosurgery. <i>Asenjo, A.</i>	357
Cranial Trephining in Ancient Peru. <i>Trelles, J. O., and Fernandez, E.</i>	359
The E.E.G. in the Diagnosis and Localization of Cerebral Neoplasms. <i>Villavicencio, C. C., and Piedrahita, R.</i>	425

DECEMBER.

Treatment of Depression and of Agitation with d-Desoxyephedrine Chloride. <i>Delgado, H., and Carillo-Broatch, A.</i>	539
The Syndrome of Hemiballismus. <i>Trelles, J. O., et al.</i>	554
Classification of the Responses to the Rorschach Test. <i>Sal y Rosas, F., et al.</i>	567

REV. PSICOL. GEN. APLIC.

VOL. V.	1950.
The Reason for the Existence of the Psychotherapy of Alfred Adler. <i>Kohlmann, T.</i>	693
The Vocabulary of the Stanford-Binet Test in El Salvador. <i>Gaw, E. A.</i>	701
A Scheme for the Diagnosis of the Biotypes of Kretschmer. <i>de Ormacchea, J. L., and Höhne, K.</i>	731

RIV. PAT. NERV. MENT.

VOL. LXXII.	1951.
Detailed Nervous Structure in the Body of the Extrinsic Eye Muscles in Man. <i>Otonello, P.</i>	261
The Histological Problem of Encephalomyelitis. <i>Cardona, F.</i>	265
A Case of Verbal-motor Epilepsy from the Point of View of E.E.G., Neurosurgery and Anatomy. <i>Galrici, E.</i>	289
Orbicular and Palpebral Reflexes in Normals, Neurotics and in Parkinsonism. <i>Chiaramonti, E.</i>	310
Considerations of Pyramidal Hypertonia in Connection with a Peculiar Gait in Multiple Sclerosis. <i>Reale, G.</i>	222
The Action of Malonitrile on the Brain of Rabbits. <i>Reale, G., and D'Argenio, L.</i>	331
A Case of Myodystonic Syndrome Treated by Commissural Myelotomy. <i>Nistri, M.</i>	342
Anatomo-pathological and Chemical Research into a Case of Salvarsan Encephalopathy. <i>Fortina, A.</i>	348
Fibrinolysis During Convulsions. <i>Barucci, M.</i>	361
Commissural Myelotomy. <i>Piazzesi, W.</i>	383
Puerperal Hemiplegia. <i>D'Argenis, L.</i>	402
Comparison Between Biological-Humoral Modifications Immediately Following an Epileptic Fit, Therapeutic Shock and Adrenalin Stimulation of the Sympathetic. <i>Barucci, M.</i>	411

SCHW. ARCH. NEUR. PSYCHIAT.

VOL. LXVII.	1951.
The Psychiatric Indications for the Interruption of Pregnancy. <i>Binder, H.</i>	245
The Physiology and Pathology of the Rhinencephalon. <i>Bornstein, B.</i>	264
Music and Psychotherapy. <i>Frey, E.</i>	274
A Question of Nervous Disease from Acute Porphyria. <i>Grogg, E.</i>	292
Statistical Data on Multiple Sclerosis. <i>Meggyeshazy, J.</i>	323
A Case of Traumatic Chorea. <i>Moffie, D.</i>	327
The Leucotomy Clinic. <i>Muller, M.</i>	338
Experience with Leucotomised Schizophrenics. <i>Rorschach, W-U.</i>	355
Psychiatric Investigation of the Results of Artificial Interruption of Pregnancy. <i>Siegfried, S.</i>	365
The Importance of Various Pyramidal Reflexes, etc. <i>Stachelin, B.</i>	389
The Nightmare. <i>Stern, A.</i>	405

1. Biochemistry, Pathology, etc.

Cholinesterase of Red Cells in Mental Diseases. *Barbato, L., and Terrana, V.* [*Acta neurol (Naples)*, **5**, 429-37 (1950).]

The cholinesterase content of red cells is lower in women than in men, is substantially lower in catatonic, hebephrenic and simple schizophrenia and in biopathic or cerebropathic phrenasthenias, has a trend to decrease in progressive paralysis, and is normal in paranoid schizophrenia, in dysthymias, and other phrenasthenias.

C. SCANDURA (Chem. Abstr.).

Cholinesterase in Encephalitic Parkinsonism. *Barbato, L.* (Univ. Palermo, Italy), and *V. Terrana.* [*Lavoro neuropsichiat.*, **7**, 9 pp. (1950 (reprint).]

In 19 patients the cholinesterase of red cells was low (5.04 in men, 4.80 in women, in c.c. 0.01 N NaOH per c.c. blood as in method of following abstract). The

decrease was greater in patients to whom belladonna was administered. Red blood cells taken from the side attacked by the syndrome showed lower values than cells from the other side.

C. SCANDURA (Chem. Abstr.).

Factors Affecting Acetylcholine Found in Excised Rat Brain. Elliott, K. A. C., and Henderson, Nora, (McGill Univ., Montreal, Can.). [*Am. J. Physiol.*, **165**, 365-74 (1951); cf. *C. A.*, **44**, 10179b.]

The amount of acetylcholine (I) found in rat whole brain does not change rapidly after excision; in cortex it falls with time. Less (I) is found in brains of small than of large animals. Freezing in liquid air causes loss of (I). This does not occur in brains from eserized animals. The (I) content of brains of eserized animals is elevated. Virtually all the (I) in brain is in the bound form. Acid, mechanical disturbance, freezing, hypotonic suspension medium, and high K concentrations accelerate liberation from the bound form. The release of (I) from the bound form appears to be reversible. The possibility is discussed that bound (I) is not necessarily an intermediate in the production of free (I), and that the (I)-synthesizing system may be located on the cell surface.

E. D. WALTER (Chem. Abstr.).

The Presence of a Reticulocytogenic Factor in the Cerebrospinal Fluid (CSF). Agostini, Luciano (Univ. Perugia, Italy). [*Riv. Biol. (Perugia)*, **42**, 339-55 (1950) (English summary).]

Normal rabbits intravenously injected with 1 c.c. centrifuged CSF taken from bled rabbits showed a high reticulocytosis in the peripheral blood. This did not occur when the CSF was taken from normal rabbits. Therefore there may be a reticulocytogenic factor in the CSF.

C. SCANDURA (Chem. Abstr.).

The Precipitation of Cerebrospinal Fluid Globulin by Zinc Sulfate. Donovan, Alfred M., Foley, Joseph M., and Moloney, William C. (Boston City Hosp., Boston, Mass.). [*J. Lab. Clin. Med.*, **37**, 374-81 (1951).]

The method is based on that described by Kunkel (*C. A.*, **42**, 1620i) for the study of serum proteins. Results of the test correlate well with the presence of neurosyphilis and multiple sclerosis. The procedure may be useful in measuring the degree of activity of the disease process in multiple sclerosis.

FRED H. SNYDER (Chem. Abstr.).

Chlorides in Spinal Fluid in Normal and Pathological Conditions. Trautman, S., and Ambard, L. [*Bull. acad. natl. med.*, **135**, 105-7 (1951).]

Capillary ultrafiltration supplies the meningeal space with a fluid closely resembling plasma in electrolyte concentration. In the process of circulation fluid is selectively filtered out of the system, leaving a higher concentration of Cl in the remaining fluid. A similar condition exists in the aqueous humor of the eye.

A. E. MEYER (Chem. Abstr.).

Glutamic Acid and Intelligence Quotient. Delay, Jean, and Pichot, P. [*Bull. Acad. natl. m  d.*, **135**, 112-17 (1951).]

Modification of the metabolism of the nerve cells improves the intelligence output.

A. E. MEYER (Chem. Abstr.).

Cell Content of Cerebrospinal Fluid. Bedford, T. H. B. [*Brit. J. Pharmacol.*, **3**, 80-3 (1948).]

The cell content of the cerebrospinal fluid was determined 24 hours after the introduction of procaine, amylocaine and amethocaine into the cisterna magna of dogs; the effects were compared with those produced by distilled water, isotonic NaCl, and Ringer solution. Isotonic NaCl solution, 1 per cent. procaine, and amylocaine-HCl in distilled water excited reactions of approximately equal intensity. Ringer solution caused a more intense reaction than distilled water, but less than that of isotonic NaCl solution. The result of these experiments raises doubts about the advisability of using simple NaCl to render isotonic solutions required for introduction into the subarachnoid space.

B. A. (Chem. Abstr.).

Significance of Glutamic Acid for the Metabolism of Nervous Tissue. Weil-Malherbe, H. (Runwell Hosp., Wickford, Essex, Engl.). [Physiol. Revs., **30**, 549-68 (1950).]

The 3 enzymic reactions involving glutamic acid (deamination, transamination, amidation) may perhaps be integrated into a system for the deionization and removal of intracellular NH_3 . Glutamic acid is the only amino acid oxidized in the brain to any appreciable extent by a specific enzyme. Transamination of glutamic acid serves as a buffer system which takes up the sudden influx of NH_3 and ensures its gradual disposal during restitution. The amidation reaction is formulated as follows: glutamic acid + NH_3 + ATP $\rightarrow$ glutamine + ADP + H_2PO_4 . Glutamic acid is known to maintain respiration of nervous tissue. It may also be essential for sustaining its function. Glutamic acid may exert its special activity through its effect on permeability of the nerve cell membrane. The latter may become increased, allowing diffusion from the cell, which can be prevented by the joint action of glucose and glutamic acid. As far as the effect of glutamic acid in hypoglycemia is concerned, the evidence seems to point to an adrenergic stimulation. Similarly, the effect of glutamic acid in the treatment of *petit mal* or of mental deficiency is believed to be by an adrenergic mechanism just as in the case of amphetamine (sympathomimetic amines). In fact, a comparison of their effects manifests such a degree of parallelism as to suggest a fundamental identity of the underlying mechanism.

S. MORGULIS (Chem. Abstr.)

Relation Between the Adaptation-tropic Filaments of Sympathetic Nervous System and the Adrenals. Senkevich, I. V. (Kazan Sect., Acad. Sci.). [Fiziol. Zhur. S.S.S.R., **36**, 558-65 (1950).]

The source of sympathin in animals appears to be adrenaline circulating in the blood. In the absence of sympathin the sympathetic nervous system loses the ability to transmit through its adaptation-tropic fibres the impulses to the appropriate tissues.

G. M. KOSCLAPOFF (Chem. Abstr.)

Effect of Vegetative Nervous System on the Recoil Reflex. Gumenyuk, I. G. (Dnepropetrovsk State Univ.). [Fiziol. Zhur. S.S.S.R., **36**, 552-7 (1950).]

Deposition of a NaCl crystal on the thalamic region of the brain causes the disappearance of the recoil reflex, caused by Faradic stimulation of the central end of sciatic nerve. The phenomenon is reversible. Ergotoxin in 1:1000 concentration does not affect the reflex, but it removes the blocking effect of the thalamic region on this reflex. The NaCl effect is manifested through the sympathetic nervous system.

G. M. KOSOLAPOFF (Chem. Abstr.)

The Effect of Estrogen on the Phosphate Turnover in the Hypophyseal-diencephalic System. Borell, U., and Westman, A. (Karolinska Sjukuset, Stockholm) [Acta Endocrinol., **3**, 111-18 (1949).]

Normal and hypophysectomized rats were treated with estradiol monobenzoate administered by intramuscular injection. P^{32} in 5 per cent. glucose solution was given 40 minutes before decapitation. The radioactivity and total phosphate of the blood, cerebellum, tuber cinereum, adenohipophysis and ovaries were determined. In normal rats estradiol monobenzoate in comparatively high doses increased the P^{32} turnover in the adenohipophysis and tuber cinereum. In hypophysectomized rats it had no significant effect on the tuber cinereum.

ELVA G. SHIPLEY (Chem. Abstr.)

Effect of Treatment with Adrenocorticotrophic Hormone (ACTH) or Cortisone on Anatomy of the Brain. Castor, C. William, Baker, Burton L., Ingle, Dwight J., and Li, Choh Hao (Univ. Michigan, Ann Arbor). [Proc. Soc. Exptl. Biol. Med., **76**, 353-7 (1951).]

In rats, administration of ACTH caused chromatolysis in the cells of the paraventricular hypothalamic nucleus. Cortisone affected this nucleus but induced more widespread chromatolysis and vacuolation of thalamic and hypothalamic nerve cells.

L. E. GILSON (Chem. Abstr.)

The Effects of Increased Potassium Concentration on the Metabolism of Rat Cerebral Cortical Slices. Lipsett, Marie Niefert, and Crescitelli, Frederick. (Univ. of California, Los Angeles). [*Arch. Biochem.*, **28**, 329-37 (1950).]

The Q_{O_2} of thin slices of cortical tissue in a glucose substrate was increased 75 per cent. by the addition of 0.1 M KCl. The effect of K was less marked in the presence of lactate and pyruvate substrates and absent with α -ketoglutarate and succinate. The addition of glutamate, citrate, α -ketoglutarate, or succinate (all participants in the tricarboxylic acid cycle) to the glucose substrate abolished the effect of K. Aspartic acid, methionine and glutamine caused no inhibition. In lactate and pyruvate media the K response was greater, on a percentage basis, at 25.5° than at 37.5°. With these substrates, glutamate inhibited the effect of K at the lower but not at the higher temperature. NaF and 2, 4-dinitrophenol inhibited the K effect, while NaN_3 did not. FRED H. SNYDER (Chem. Abstr.).

Microchemical Studies of the Nervous System. VIII. Changes in the Cystine Content of Nerve During Degeneration. May, Raoul Michel, and Thillard, Marie Jeanne (Sorbonne, Paris). [*Bull. soc. chim. biol.*, **32**, 977-82 (1950); cf. *C. A.*, **43**, 546i.].

During degeneration of the severed sciatic nerve of the rabbit the cystine content nearly doubled during the first 10 days, then slowly decreased. The relative increase in cystine was much greater than the increase in protein content of the nerve during the same period. L. E. GILSON (Chem. Abstr.).

Microchemical Studies on the Topical Distribution of Trace Elements in the Brain. Bertha, H., Malissa, H., and Pohl, F. (Tech. Hochschule, Graz, Austria). [*Mikrochemie ver. Mikrochim. Acta*, **36/37**, 988-96 (1951).]

Besides K, Ca, Na, Mg, and P, all the spectrograms show the presence of Al and Cu in the brain although their distribution in different parts of the brain is not yet known. Pb, Zn, Sr, Ag, Be and Ti also appear in the regions examined. The existence of separate cells in certain sections of the brain makes it seem possible that special elements may be required for the exercise of special functions. No definite conclusions can be drawn now. W. T. HALL (Chem. Abstr.).

The Effect of Some Antihistamines and Calcium Preparations in Disturbances of the Vascular Permeability in the Brain. Broman, Tore (Lund, Sweden). [*Intern. Arch. Allergy Applied Immunol.*, **1**, 299-305 (1951).]

Antihistamines and Ca preparations either separately or together were unable to prevent or contribute to the healing of disturbances of vascular permeability in the brain produced chemically or serologically. There is a possibility that these substances might even exert an unfavourable effect so that a site of disturbance of permeability becomes a site of punctate hemorrhage. JULIAN H. LEWIS (Chem. Abstr.).

The Histochemistry of the Corpora Amylacea of the Central Nervous System. Bravi, Giovanni, (Univ. Pavia, Italy). [*Atti soc. ital. sci. nat. e museo civico storia nat. Milano*, **86**, 14-22 (1947).]

Human brains from victims of late stages of syphilis that had been preserved in formalin for 10 years to a few hours were used. Tissue was taken from the subependymal zone of the lateral ventricles and of the third ventricle, sectioned, frozen and fixed in paraffin. Sturmer (*Histol. Histopathol. Arch.*, **5**, No. 3, 417) recorded tests showing the presence of carbohydrates in "corpora amylacea" (CA) found in such sections. Immediate study in water after staining with 0.5 per cent. toluidine blue for a few minutes showed metachromasia clearly in some of the larger CA, especially in the nucleus. A feeble test of the same sort was obtained in the nuclei of the larger CA of preparations mounted 10 hours in glycerol. This reaction shows that the composition of the CA is not homogeneous, even though doubt has been raised that it proves the presence of polysaccharide sulphates. The technique of Bignardi (*Boll. soc. med.-chir. Pavia*, **54** (1940), as well as that of Bignardi and Casella (*Boll. soc. med.-chir. Pavia*, **55**, No. 6 (1941), after 240 hours, gave a positive test for metachromasia which is more characteristic of amyloid than of mucoprotein. Tests for lipides (including phosphatides) were negative. The cortex or peripheral

part of the larger CA and the entire smaller ones are composed of undifferentiated material, from which, as the CA grow, the organized materials of the nucleus are formed. The nuclei of the larger CA have in addition to the characteristics of the cortex the ability to react as H_2SO_4 -esters of the higher polysaccharides.

E. L. GREEN (Chem. Abstr.).

Oxygen Consumption of the Cerebrum. Covián, F. Grande. (Univ. Madrid). [Rev. clín. españ., **39**, 1-17 (1950).]

L. E. GILSON (Chem. Abstr.).

Biochemical Studies on the Action of the Nerve. II. The Distribution of Cholinesterase in Animal Brains. Okinaka, Shigeo, Yoshikawa, Masaki, and Gotô, Jûya. (Univ. Tokyo). [Igaku to Seibutsugaku (Med. and Biol.), **18**, 38-40 (1951); cf. C. A. **45**, 1181c.]

Cholinesterase activities in various parts of brains of rats, rabbits and dogs were determined with results closely agreeing with those of Nachmansohn (C. A. **33**, 7322⁸). The enzyme activity was fairly constant in one part of brain in one species of animal, although significant differences were observed between the enzyme activities of various parts of one animal or of one part of various species. The enzyme activities in the brains of rats inoculated with Yoshida's sarcoma showed no appreciable difference from those of normal rats, although the enzyme activities in the liver and serum were lowered by 20-30 per cent.

M. N. (Chem. Abstr.).

Glutamic Acid Decarboxylase in Brain. Roberts, Eugene, and Frankel, Sam. (Washington Univ., St. Louis, Mo.) [J. Biol. Chem. **188**, 789-95 (1951); cf. C. A., **45**, 3431g.]

Glutamic acid decarboxylase was demonstrated in homogenates and acetone powders from mouse brain. The enzyme is a typical decarboxylase. It requires pyridoxal phosphate as coenzyme and is inhibited by semicarbazine and NH_2OH . When excess glutamic acid and pyridoxal phosphate are present the reaction is of zero order and the activity is proportional to the quantity of enzyme used.

FELIX SAUNDERS (Chem. Abstr.).

Phosphate Transport and Turnover in the Brain. Sacks, Jacob, Culbreth, Geo. G., and Damast, Barbara. (Brookhaven Natl. Lab., Upton, N.Y.). [Am. J. Physiol., **165**, 251-6 (1951).]

A comparison was made of the distribution of intracisternally and intravenously injected tracer phosphate between brain, blood plasma, and muscle in cats. In 4 hours after the injection into the cisterna magna, about 60 per cent. of the tracer appears to be absorbed into the general circulation. There is a very rapid interchange of phosphate between the cerebrospinal fluid and the brain substance, with a high rate of incorporation of the tracer into the phosphocreatine and the labile P of the adenosine triphosphate (ATP) of the brain. The apparent turnover rate of the phosphocreatine and ATP of brain following the intravenous injection of the tracer is higher than the turnover rate of these compounds in resting muscle. The intravenously injected tracer becomes available to the brain substance for turnover by secretion into the cerebrospinal fluid.

E. D. WALTER (Chem. Abstr.).

Tetanus Intoxication and its Effect on the Metabolism of Central Nervous Tissue. Asakura, Shintarô, Takaki, Masahiko, Kinashi, Atsuo, and Higashiyama Akira. (Osaka Univ.). [Osaka Daigaku Igaku Zasshi, **2**, 395-405 (1950).]

Reducing sugars, acetone bodies, pyruvate and α -ketoglutarate in the spinal fluid and blood of rabbits poisoned with tetanus were estimated. The amount of glucose and total acetone bodies in both blood and spinal fluid increased as the tetanus paralysis proceeded. The rate of increase in spinal fluid was greater than that in blood. The increase in β -hydroxybutyrate and acetoacetate accounted for most of the increase in the acetone bodies. Acetoacetate began to increase before β -hydroxybutyrate increased. Pyruvate and α -ketoglutarate increased in parallel with the intoxication. The increase of α -ketoglutarate was earlier in the spinal

fluid than in blood, as was that of pyruvate. The return of these metabolites to normal levels was much earlier than the recovery from paralysis.

ITIRO TYUMA (Chem. Abstr.).

Multiple Sclerosis: A Correlation of its Incidence with Dietary Fat. Swank, Roy Laver. (McGill Univ., Montreal, Can.). [Am. J. Med. Sci., **220**, 421-30 (1950).]

An epidemiologic study of multiple sclerosis in Europe and unreported clinical studies indicate that a diet high in fat, although not the cause of multiple sclerosis, may contribute to a high incidence of the disease by accelerating it in susceptible individuals.

MARION HORN PESKIN (Chem. Abstr.).

The Localization of Cerebral Tumors with Radioactive Derivatives of Fluorescein. Belcher, E. H., and Evans, H. D. [Brit. J. Radiology, **24**, 272-9 (1951).]

It is possible to detect lesions concentrating (I)¹³¹ with the scintillation counter described, provided that the concentration of activity in the lesion is 10 times that of normal brain, and the size of the lesion is greater than a certain minimum volume depending on its depth. The syntheses of diiodo¹³¹ fluorescein and of dibromo⁸² fluorescein are described.

G. L. CLARK (Chem. Abstr.).

Presence of Histamine in Extracts of the Central Nervous System. Cicardo, Vicente H., and Stoppani, A. O. M. [Pubs. centro invest. fisiol. (Buenos Aires), **13**, 153-65 (1950).]

The mechanism of the action of brain extracts on arterial pressure, respiration and pupillary diameter in the dog was studied. The active reagent of the action of the extracts has the following properties: (a) It is inhibited by antihistaminic benadryl to the same extent as histamine; (b) it is not affected by atropine; (c) like histamine, it is not precipitated by Pb salts, but it is precipitated by Ag in alkali solution of Ba(OH)₂ and by phosphotungstic acid in acid medium, while the hypotensor action of the active fractions is inhibited by benadryl. The hypotensor agent is extracted from the cerebral tissue by alkali, acetone, and CCl₃CO₂H. These findings indicate that histamine is the principal reagent of the pharmacological action of the extracts of the central nervous system of the dog. The histamine equivalent of the nervous tissue is approximately 15-20 γ/gm. of the fresh tissue. The hypotensor effects of brain extracts, peduncles and bulb are similar, while the effects obtained with cerebellar extracts are less marked. The hypotensor action of brain extracts of different types of animals are analogous.

W. R. EICHLER (Chem. Abstr.).

The Decerebration Rigidity of Bufo arenarum as Test for Curarizing Substances. Patetta, M. A. (Facultad med., Montevideo, Uruguay). [Arch. soc. biol. Montevideo, **16**, 91-4 (1949) (pub. 1950).]

The rigidity shown by decerebrated *Bufo arenarum* disappeared after subcutaneous injection of crude curare, flaxedil, or intocostin T in a few minutes. This reaction is recommended as a test for curarizing substances.

F. FROMM (Chem. Abstr.).

The Neuropathology of Antibiotic-induced Peripheral Nerve Paralysis. Woodhall, Barnes, Broadbent, Thomas R., and Javer, Jerome (Duke Univ., Durham, N. C.). [Surg. Forum, Proc. 36th Clin. Congr. Am. Coll. Surgeons, 1950, 394-9 (pub. 1951).]

Reports of paralysis and neuritis from injections of antibiotics are discussed. The sciatic nerve of the cat was injected subepineurally with 100,000 units of Na, K, or Ca salts of penicillin or 25-75 mgm. of dihydrostreptomycin sulfate, or otherwise treated with other agents used in injecting antibiotics intramuscularly. Histological studies were made after 10 and 60 days. The penicillin salts had a toxic effect upon the peripheral nerve axon, which might lead to axonal degeneration. With sesame oil or peanut added as a carrier, toxicity was increased. The dihydrostreptomycin sulfate had an even more marked effect. Tween 80, pectin, and carboxymethylcellulose had little effect. Care must be taken to avoid major peripheral nerve segments when antibiotics are injected intramuscularly.

W. C. TOBIE (Chem. Abstr.).

Effect of Adenosinetriphosphoric Acid on the Chronaxy of the Motor Zone of the Cerebral Cortex. Babški[†], E. B., and Malkiman, I. I. [*Doklady Akad. Nauk S.S.S.R.*, **74**, 1135-7 (1950).]

Suboccipital administration of adenosine triphosphate (as Na salt) to dogs leads to the following results: Repeated use of small doses (10-20 mgm.) lowers the rheobase by 20-45 per cent. and the chronaxy by 40-60 per cent. within 3-5 minutes, after which both begin to return to substantially normal levels within about 80 minutes. Use of large doses (30-50 mgm.), however, causes a convulsion stage, after which the sensitivity of the cortex declines (rheobase rises) and the chronaxy is extended; maximum values reach 120-45 per cent. and 130-60 per cent., respectively after some 30 minutes, after which a decline to normal gradually takes place. Larger doses cause convulsions and death. Administration of 15-20 mgm. into the blood-stream gives qualitatively the same results as the suboccipital method, but the effect is seen after 1-2 hours; this occurs only in intra-arterial administration; the intravenous method gives no changes in the cortex. It appears that ATP plays a significant role in determination of the level of sensitivity of the cortex and in the rapidity of response to a stimulus.

G. M. KOSOLAPOFF (Chem. Abstr.).

Blood Flow and Oxygen Consumption of the Human Brain in Diabetic Acidosis and Coma. Kety, Seymour S., Polis, B. David, Nadler, Carl S., and Schmidt, Carl F. (Univ. of Pennsylvania, Philadelphia). [*J. Clin. Invest.*, **27**, 500-10 (1948).]

Studies of blood gases, electrolytes, acid-base balance, respiration, blood pressure, cerebral blood flow and cerebral O consumption are reported in 14 patients in severe diabetic coma, 6 of which were in deep coma. Respiratory minimum volume was well correlated with arterial pH. Coma was associated with, and probably the result of, a 40 per cent. reduction in cerebral utilization of O, which occurred in spite of a generally augmented cerebral blood flow and normal arterial O saturation. The depression in cerebral O consumption is partly related to the acidosis, and more significantly to the ketosis, although other factors as yet poorly defined are undoubtedly operating. The results establish the feasibility of applying these techniques to diabetic coma, and open the possibility of further defining the biochemical derangements in the living human brain by study of new specific metabolic components.

JOHN T. MYERS (Chem. Abstr.).

Anaerobic Glycolysis of the Warm-blooded Brain in situ. Thorn, Werner (Univ. Kiel, Ger.). [*Biochem. Z.*, **321**, 361-7 (1951).]

Since at the moment of decapitation there is still O available in the brain (0.3 volume per cent. in solution, the O as oxyhemoglobin also creatin phosphate as a source of energy), it is calculated that there is enough energy available to meet the resting needs of the brain over the first 10 seconds. Within 7 to 25 seconds the anaerobic glycolysis exceeds by far the values obtained *in vitro* with carcinomas. The anaerobic glycolysis is the same whether the animal is awake or under urethan narcosis. Within the 7-25-second period the maximum rate of glycolysis is 70-90 mgm. per cent. per minute, but between 20 and 100 seconds the lactic acid production proceeds at a uniform rate of 33 mgm. per cent. per second. After 100 seconds glycolysis slows down chiefly because of lack of substrate. The maximum glycolysis may coincide with the convulsions associated with ischemia.

S. MORGULIS (Chem. Abstr.).

Effect of Ascorbic Acid on the Gaseous Metabolism of the Animal Brain. Uzbekov, G. A. (Med. Inst., Stavropol). [*Biokhimiya*, **16**, 104-7 (1951).]

Vitamins B₁, B₂ and nicotinic acid can correct the unbalance in carbohydrate and gas metabolism of the animal brain brought about by a prolonged carbohydrate diet (*Trudy Stavropol'skogo Medinstituta*, **3**, 115 (1949)). When the dog is saturated with ascorbic acid (I) by daily subcutaneous injection of 20 mgm. (1)/kgm., the O content increases in the arterial blood and decreases in the venous blood. The coefficient of O utilization in the brain rises from 28 to 52 per cent. The hemoglobin content of dog blood increases from 13.6 to 13.9 per cent. The amount of (I) produced by the dog is apparently insufficient for the maximum utilization of the biochemical processes.

H. PRIESTLEY (Chem. Abstr.).

Determination of Anaerobic Glycolysis of Rabbit Brain in situ. Bredow, Wolfgang and Thorn, Werner (Univ. Kiel, Ger.). [Biochem. Z., **321**, 357-60 (1951).]

Rabbit heads were either frozen with liquid air after variable periods following decapitation or the brain was separated into two halves, one being frozen immediately (control), the other after a determined interval. In both series it was observed that there was an increase in bisulfite-binding substances. Methods for determining lactic acid are discussed. The fact that there is actually a rise in lactic acid has been further corroborated by the observation that following an intravenous injection of CH_2ICOOH there was no increase. S. MORGULIS (Chem. Abstr.).

Isolated Nuclei from Cells of the Cerebral Cortex. Preparation and Enzyme Content. Richter, D., and Hullin, R. P. (Neuropsychiatric Research Centre, Whitchurch, Cardiff, Engl.). [Biochem. J., **48**, 406-10 (1951).]

Nuclei were isolated from cerebral cortex by differential centrifugation. They were found to contain a high concentration of alkaline phosphatase. This bears out previous studies showing an intense alkaline phosphatase reaction of the chromosomes. This enzyme is probably responsible for P exchange in desoxyribonucleic acid. The acid phosphatase is present in equal concentrations in nucleus and cytoplasm of the nerve cell, but its biochemical significance is not understood. Cholinesterase was also found in high concentration. The cytochrome oxidase activity is minute, but is approximately of the same order of magnitude as in the cytoplasm. The carbonic anhydrase activity of the nuclei is roughly about one third of that of cytoplasm but, as is pointed out, the physiological significance of the enzyme is not sufficiently known to interpret this finding correctly.

S. MORGULIS (Chem. Abstr.).

2. Pharmacology and Treatment.

Effects of Pentobarbital, Amobarbital, and Barbitol on Oxygen Consumption of Brain Slices. Westfall, B. A. (Univ. of Missouri, Columbia). [J. Pharmacol. Exptl. Therap., **101**, 163-6 (1951); cf. C. A., **43**, 7139d.]

Pentobarbital (0.3 mgm. per cent.), amobarbital (1 mgm. per cent.), and barbitol (2 mgm. per cent.) slightly increased the O consumption of rat brain slices. Considerably higher concentrations decreased O consumption.

L. E. GILSON (Chem. Abstr.).

A 24-hour Periodicity in the "LH-Release Apparatus" of Female Rats, Disclosed by Barbiturate Sedation. Everett, John W., and Sawyer, Charles H. (Duke Univ., Durham, N. C.). [Endocrinology, **47**, 198-218 (1950).]

The specific neurogenic stimulus which is essential for the ovulatory discharge of LH (luteinizing hormone) and which activates the hypophysis between 2 and 4 p.m. on the day of proestrus, and a 24-hr. rhythm of excitability in the neural component of the LH-release apparatus, have been confirmed. Nembutal will prevent the ovulatory activation of the hypophysis when administered at 2 p.m. during proestrus. Follicles persist for 2 to 3 days when nembutal is repeated on successive afternoons at the same critical hour. On the second and third days a supplementary injection is required at 3:30 and 4 p.m. If treatment is omitted or postponed until after 4 p.m. on either of these three days, pituitary activation occurs and ovulation will follow. Amytal, dial, barbitol and phenobarbital produce similar results. Blockage of LH release with barbiturates on successive days discloses a follicular cycle which ends in atresia approximately two days before the onset of the next proestrus.

ELVA G. SHIPLEY (Chem. Abstr.).

Effect of Barbiturates on Oxidative Phosphorylation. Brody, Theodore M., and Bain, James A. (Univ. of Illinois Med. School, Chicago). [Proc. Soc. Exptl. Biol. Med., **77**, 50-3 (1951).]

Thiopental, pentobarbital and amobarbital lower the phosphate uptake/O uptake ratio obtained in particular tissue preparations from liver and brain respiring on a pyruvate substrate. This depression is obtained at concentrations of the drugs which have only a slight effect on the O uptake of the preparations, and which

approximate those necessary *in vivo* to produce surgical anesthesia. It may be that such an uncoupling of phosphorylation from oxidation is one way in which barbiturates act to produce anaesthesia. L. E. GILSON (Chem. Abstr.).

The Metabolism of Tetraethylthiuram Disulfide (Antabuse, Aversan) in the Rat, Investigated by Means of Radioactive Sulfur. Eldjarn, L. (Univ. Oslo, Norway). [Scand. J. Clin. Lab. Invest., **2**, 198-201 (1950); cf. following abstract.]

Approximately 80 per cent. of ingested antabuse (I) (tagged with S³⁵) is absorbed from the intestinal tract of the rat, the remaining 20 per cent. being excreted in the feces. Only 60 per cent. of intraperitoneally injected (I) is recovered in the urine and feces in the following 15 days. (I) accumulates primarily in the adrenals, liver and spleen. BERNARD KLEIN (Chem. Abstr.).

The Metabolism of Tetraethylthiuram Disulfide (Antabuse, Aversan) in Man. Investigated by Means of Radioactive Sulfur. Eldjarn, L. (Univ. Oslo, Norway). [Scand. J. Clin. Lab. Invest., **2**, 202-8 (1950); cf. preceding abstract.]

Ninety per cent. of antabuse (I) is absorbed from the intestine, the remainder is excreted in the feces. The greater part of (I) is oxidized by the organism and excreted in the urine as part free and part sulfated, although small amounts are excreted unchanged or in reduced form as diethyl dithiocarbamate (II). Twenty per cent. of absorbed (I) remains in the body after 6 days. The optimum plasma concentration of (I) is 0.5-1.0 mgm. per cent. and exists almost entirely as free (I) and after 6 hours two-thirds is reduced to (II). The suggestion is made that the physiological effect may be due to the (II) anion. B. KLEIN (Chem. Abstr.).

Anticonvulsive Action and Molecular Structure of Some Heterocyclic Pentagonal Compounds. VIII. Influence of Opening of the Cycle. Hazard, René, Cheymol, Jean, Chabrier, Peirre, and Smarzewska, Klaudia, [Compt. rend., **232**, 658-60 (1951); cf. C. A., **44**, 3613i.]

In explaining their anticonvulsant properties, Goodman *et al.* (C. A., **43**, 4763f) advanced the theory that the hydantoins and barbiturates are transformed in the organism by opening of the cycle into an active linear chain, whereas the *acylureas* show a similar activity on forming a cycle *in vivo*. When the hydantoins and thiohydantoins were paired with their corresponding acylureas, and tested for protection against pentazole and electric shocks, it was found that Goodman's theory holds for the hydantoins and thiohydantoins, but not for phenacetylurea. Diphenylhydantoin, which is inactive in pentazole crisis, is very effective in electric shock, inverting its effect in the molecule corresponding to an open cycle. The cyclization of monophenylacetylurea is very active in both tests, while monophenylhydantoin is inactive in both crisis.

DOROTHY A. MEYER (Chem. Abstr.).

Antagonism and Synergism Between Narcotics and Sympathomimetic Amines in their Action on Central Nervous System of Vertebrates. III. Role of Sympathetic Nervous System on Narcotic Action and Phenylalkylamine Action on Central Nervous System of Cold-blooded Animals. Ya, S. [Arbuzov. Fizio. Zhur. S.S.S.R., **36**, 496-509 (1950); cf. C. A., **43**, 7141g.]

In a study of normal and sympathectomized frogs the minimum a.c. current that caused tetanic convulsions was determined. In normal animals the increased value of the minimum current under influence of the chemical agents places the latter in the following descending order of activity: pervitin, phenamine, ephedrine, sympatol, adrenaline; in sympathectomized frogs the order is pervitin, phenamine, adrenaline, ephedrine, sympatol. Duration of action of narcotics in intact animals is lowered by small and moderate doses of phenylalkylamines (more effective with chloral hydrate than with medinal). Antagonism to narcotics is strongest with phenamine, pervitin, and ephedrine; at high dosages narcotics and phenylalkylamines are synergistic. In sympathectomized animals the antagonism is weak and at medium or high dosage only synergy is observed.

G. M. KOSOLAPOFF (Chem. Abstr.).

Selective Inhibition of Brain Respirations by Benadryl. Carlisle, Edith M., and Crescitelli, Frederick (Univ. of California, Los Angeles). [*Science*, **112**, 272-3 (1950).]

The O consumption of slices of rat cerebral cortex respiring in a Krebs-Ringer phosphate solution (pH 7.35) was studied with glucose and L-glutamate as substrate, and with and without benadryl-HCl(I) and histamine. With glucose, the addition of (I) exerted no effect on O consumption, but with L-glutamate respiration was completely blocked. The selectivity was specially striking when (I) was used in concentration range of 0.0004-0.0018 M. The endogenous respirations (no added substrate) behaved, in response to (I), not like respiration in glucose but like respiration in L-glutamate. Results similar to the above were obtained with pyribenzamine-HCl and with histadyl. N-amyl carbamate, dl-amidone and morphine did not show the selective action of (I), the same inhibition being obtained in both glucose and L-glutamate media. Histamine-2 HCl in 0.03 M concentration did not influence the O respiration of brain slices in glutamate, nor prevent the inhibition of respiration by (I). The possibility exists that some metabolic step in the oxidation of L-glutamate is blocked.

JULIA O. HOLMES (Chem. Abstr.).

Effects of Repeated Convulsions from Electroshock on Some Blood Enzymes. Tripodo, Cesare (Univ. Bari, Italy). [*Riv. biol. (Perugia)*, **42**, 485-502 (1950).]

In rabbits electro-shocked every day for 40 days (1) the amylase power of blood (determinations by the Wohlgemuth method) decreased 50 per cent. in 3 of 5 cases from the 20th day of treatment up to the 20-30th day after cessation of shocks; (2) the phosphatase power of blood (Roberts method, *C. A.*, **24**, 3269) decreased irregularly during the 10-20th days, normal values being restored and surpassed, respectively, at the end of and 30 days after the treatment; (3) the P content of blood (Briggs method, *C. A.*, **18**, 2183) decreased from 3.7 to 2 mgm. per cent. within the 20th day, normal values restored and surpassed (26-85 per cent.) after the treatment; (4) the tributyrinase power of plasma (Scoz and Guzzi method, *C. A.*, **36**, 7044⁶) decreased between the 7th and 14th day, normal values restored, surpassed (up to 41.98 per cent.) and again restored, respectively, on the 21st day, 16-30 days after, and 60 days after the shock treatment. C. SCANDURA (Chem. Abstr.).

Inhibitory Action of Carbon Dioxide on Experimental Convulsions. III. Experiments on Cryoepilepsy in the Frog: Mechanism of the Inhibitory Action of Carbon Dioxide on Convulsions. Moussatché, H. [*Mem. inst. Oswaldo Cruz*, **48**, 227-37 (1950) (in English); cf. *C. A.* **38**, 1032⁸.]

Frogs whose intercellular fluid pH is lowered by perfusion below the pH obtained after CO₂ inhalations sufficient to inhibit cryoepilepsy are still subject to such convulsions. It is therefore likely that CO₂ has a specific inhibitory action on the nervous centers and does not inhibit cryoepilepsy merely by lowering intercellular fluid pH.

KARL F. URBACH (Chem. Abstr.).

Anticonvulsants and their Effect on Mouse Convulsions. Cheymol, Jean, and Thuillier Jean (Faculté med., Paris). [*Arch. intern. pharmacodynamie*, **83**, 593-601 (1950).]

Drugs were tested against strychnine, pentrazole, picrotoxin, and thujone convulsions in mice. They were effective in decreasing order: 5, 5-dimethyl-2, 4-dithiohydantoin, phenobarbital, 3, 5, 5-trimethyl-2, 4-oxazolidinedione, phenyl-acetylurea, and 5, 5-diphenylhydantoin. The protection provided by the first was almost complete, and at 100 mgm./kgm. there were no toxic symptoms. Diphenylhydantoin was almost useless. Picrotoxin convulsions were the most resistant to the action of these protective drugs.

M. L. C. BERNHEIM (Chem. Abstr.).

Central Nervous Function and Changes in Brain Metabolite Concentration: Characteristic Glycogen Increment Patterns Produced by Convulsant Drugs. Chance, M. R. A. (Univ. Birmingham, Engl.). [*Brit. J. Pharmacol.*, **6**, 1-7 (1951); cf. *J. Exptl. Biol.*, **27**, 311 (1950).]

Low variance associated with the determination of glycogen (I) in mouse brain during procedures which bring about changes in the amount of (I) permitted accurate

estimations of relative changes in different parts of the brain. The accumulation of (I) in mouse brain, which takes place during convulsions, was determined in cortex, midbrain, medulla, spinal cord, central lobes and the lateral lobe of the cerebellum at various times during seizures induced by dl-amphetamine, caffeine, dibenamine, insulin, leptazole, coramine, picrotoxin, Na diphenylhydantoin and strychnine. In general, the most marked increases in (I) were found in cortex, mid-brain, and medulla. The resulting patterns showed differences in the rates of increment and recovery for different parts of the brain and for different drugs. These patterns were interpreted as indicating the distribution of nervous activity in the brain arising from drug stimulation.

RICHARD F. RILEY (Chem. Abstr.).

Effect of Amphetamine on Conditioned Behaviours. Yoshii, Naosaburo, Sasaki, Hiromasa, and Hiraoka, Keizo (Osaka Univ.). [Med. J. Osaka Univ., **2**, 151-4 (1950).]

Small doses of amphetamine (I) caused an increase in conditioned salivary secretion (but not of unconditioned salivary secretion) in the dog. Larger doses of (I) inhibited the conditioned salivary secretion. (I) heightens excitability level of conditioned reflex center and decreases the fatigue produced by the repetition of the reflex performance. Large doses of (I) cause the experimental animal to take neither food nor water.

DON SCOTT (Chem. Abstr.).

Effect of Sodium Salicylate and Acetylsalicylate on Metabolism of Rat Brain and Liver in Vitro. Fishgold, J. T., Field, J., and Hall, V. E. (Stanford Univ., Stanford, Calif.). [Am. J. Physiol., **164**, 727-33 (1951).]

Na salicylate, added to the medium in which slices of rat cerebral cortex are suspended, increases the O consumption in concentrations up to 0.56 millimols per l., and decreases it in higher concentrations. Na acetylsalicylate is without effect. Anaerobic glycolysis of brain tissue was not affected either by salicylate in moderate concentrations. Liver slice O consumption is not changed by concentrations of Na salicylate up to 0.62 millimols per l., but is increased by comparable concentrations of Na acetylsalicylate. Possible mechanisms for the different metabolic response of brain and liver tissue to the salicylates are discussed, and the bearing of the results on a hypothesis of temperature regulation attempting to relate antipyretic action to changes in brain metabolism is considered.

E. D. WALTER (Chem. Abstr.).